Papers

Effects of transfusion with red cells filtered to remove leucocytes: randomised controlled trial in patients undergoing major surgery

Joost A van Hilten, Leo M G van de Watering, J Hajo van Bockel, Cornelis J H van de Velde, Job Kievit, Ronald Brand, Wilbert B van den Hout, Robert H Geelkerken, Rudi M H Roumen, Ronald M J Wesselink, Ankie W M M Koopman-van Gemert, Jan Koning, Anneke Brand for Tactics (transfusion associated complications study)

Abstract

Objective To compare postoperative complications in patients undergoing major surgery who received non-filtered or filtered red blood cell transfusions.
Design Prospective, randomised, double blinded trial.
Setting 19 hospitals throughout the Netherlands (three university; 10 clinical; six general).
Participants 1051 evaluable patients: 79 patients with ruptured aneurysm, 412 patients undergoing elective surgery for aneurysm, and 560 undergoing gastrointestinal surgery.
Interventions The non-filtered products had the buffy coat removed and were plasma reduced. The filtered products had the buffy coat removed, were plasma reduced, and filtered before storage to remove leucocytes.
Main outcome measures Mortality and duration of stay in intensive care. Secondary end points were occurrence of multiorgan failure, infections, and length of hospital stay.
Results No significant differences were found in mortality (odds ratio for filtered *v* non-filtered 0.80, 95% confidence interval 0.53 to 1.21) and in mean stay in intensive care (−0.4 day, −1.6 to 0.6 day). In the filtered group the mean length of hospital stay was 2.4 days shorter (−4.8 to 0.0 day; P = 0.050) and the incidence of multiorgan failure was 30% lower (odds ratio 0.70, 0.49 to 1.00; P = 0.050). There were no differences in rates of infection (0.98 (0.73 to 1.32).
Conclusion The use of filtered transfusions in some types of major surgery may reduce the length of hospital stay and the incidence of postoperative multiorgan failure.

Introduction

Red blood cell transfusions are indispensable in major surgery, but they still entail potential risks for morbidity and mortality. On the other hand, beneficial effects such as better survival of allografts in kidney transplantation[1] and improved survival in patients with HIV who receive transfusions[2] are attributed to the allogeneic leucocytes.

Five randomised studies investigated the incidence of postoperative infections after abdominal surgery by comparing outcome after transfusions of non-filtered red blood cells or red blood cells with leucocytes filtered out. Three of these trials[3–5] observed a reduction and two[6 7] found a similar incidence of postoperative infections after filtered transfusions. The findings were also conflicting for other outcomes such as mortality. We investigated whether removal of allogeneic leucocytes reduces postoperative complications in patients undergoing major surgery.

Methods

On the basis of the results of a pilot study we assumed that at least 65% of the target population would be both evaluable and transfused and calculated that about 1250 patients had to be randomised.

Study design and participants

The primary outcome measures were mortality in hospital and duration of stay in intensive care. The secondary end points were incidence of multiorgan failure and postoperative infections and length of hospital stay.

Each of 19 hospitals was invited to assign patients for one or more of the three surgery groups: ruptured aortic aneurysm, elective non-ruptured aortic aneurysm surgery, and gastrointestinal oncology. We excluded patients who were aged under 18 years, had received transfusions in the three month before the date of randomisation, or had had a previous adverse reaction to blood transfusions or had specific indications for filtered transfusions.

We assessed patients before, during, and after surgery. The postoperative situation was assessed with standardised queries, daily in intensive care and weekly

Department of Immunohaematology and Blood Transfusion, Leiden University Medical Center and Sanquin Blood Supply, PO Box 9600, 2300 RC Leiden, Netherlands
Joost A van Hilten *senior research scientist*
Anneke Brand *professor in transfusion medicine*
Leo M G van de Watering *senior research scientist*
Department of Surgery, Leiden University Medical Center, Leiden
J Hajo van Bockel *professor in surgery*
Cornelis J H van de Velde *professor in surgery*
Department of Medical Decision Making, Leiden University Medical Center, Leiden
Job Kievit *professor in medical decision making*
Wilbert B van den Hout *health econometrist*

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Department of Medical Statistics, Leiden University, Leiden
Ronald Brand *statistician*
Medisch Spectrum Twente, PO Box 50000, 7500 KA Enschede
Robert H Geelkerken *surgeon*
St Joseph Ziekenhuis, PO Box 7777, 5500 MB Veldhoven
Rudi M H Roumen *surgeon*
St Antonius Ziekenhuis, PO Box 2500, 3430 EM Nieuwegein
Ronald M J Wesselink *anaesthetist*
Albert Schweitzer, Locatie Dordwijk, PO Box 306, 3300 AH Dordrecht
Ankie W M M Koopman-van Gemert *anaesthetist*
Reinier de Graaf Groep, PO Box 5011, 2600 GA Delft
Jan Koning *surgeon*
Correspondence to: J van Hilten J.A.van_Hilten@lumc.nl

Table 1 Characteristics of study population according to allocation to transfusions with filtered or non-filtered red blood cells and analysed group

Analysis group (n=1051*)	Non-filtered (n=526)	Filtered (n=525)
No (%) of women	163 (31)	168 (32)
Mean (SD) age (years)	67 (11.0)	66 (11.5)
No (%) of patients transfused	278 (53)	267 (51)
Median units/patient (25th-75th centiles)	1 (0-4)	1 (0-4)
Mean duration of surgery (min)*	210	205

*Duration of surgery was missing for 31 patients.

on the ward until the last day in hospital. We defined multiorgan failure and postoperative infection according to standard criteria.[8 9]

Transfusion products

Units of red blood cell concentrates with the buffy coat removed contained up to 8×10^8 white blood cells/unit, whereas in red blood cells filtered before storage the maximum count was 10^6 white blood cells/unit. Numbers of units that were transfused before, during, and after surgery were downloaded from the hospital blood transfusion service computer system. Patients who received products in violation of randomisation remained in the assigned arm for intention to treat analysis. We performed subgroup analysis of the transfused population, according to transfusion, to evaluate effects related to transfusion (leucocyte dose).

Results

Over 15 months, 1200 patients were randomised. The intake of patients in the study had to be stopped at the end of 2001 because of the implementation of universal leucocyte depletion of red blood cells in the Netherlands. This measure was taken by the Dutch Ministry of Health in an effort to reduce the risk of possible transmission of variant Creutzfeldt-Jacob disease in non-filtered transfusions.

Patients' characteristics

There were 1051 patients eligible for analyses (526 in the non-filtered group and 525 in the filtered arm): 79 acute aneurysm surgery, 412 elective aneurysm surgery, and 560 gastrointestinal oncological surgery. The characteristics of the patients are presented in table 1.

Number of transfusions

In the total transfused study population analysed according to intention to treat, 278 patients in the group randomised to non-filtered products and 267 patients in the group randomised to filtered products received transfusions. The median number (25th-75th centiles) of transfusions was lower than expected (1 unit (0-4 units)).

Primary end points

Mortality in hospital—Mortality in hospital was 10.3% (54 patients) in the non-filtered group and 8.4% (44 patients) in the filtered group (table 2). There was a significant reduction in mortality (0.47, 0.23 to 0.99) in favour of filtered products in the patients undergoing gastrointestinal surgery. Because this difference in mortality between 23 (non-filtered) *v* 11 patients (filtered) (8% *v* 4%) could have been caused by imbalanced randomisation with respect to age, sex, duration of surgery, number of blood transfusions, or type of surgery, we have described the gastrointestinal group in more detail in table 3.

Stay in intensive care—There was no significant difference in stay in intensive care between the randomised groups, though in the filtered group patients stayed an average of 0.4 days less (−1.6 to 0.6 days).

Secondary end points

Multiorgan failure—One hundred and sixty four patients experienced multiorgan failure (16% of the total study population). There was a significantly lower incidence in the filtered group. The overall mean odds ratio for incidence of multiorgan failure was 0.70 (0.49 to 0.99; P = 0.05).

Postoperative infections—The incidence of postoperative infections was similar in the two groups. The combined odds ratio for the three types of surgery was 0.98 (0.73 to 1.32).

Table 2 Intention to treat analyses of primary and secondary end points. Figures are totals in group (non-filtered; filtered) and odds ratios or differences in means (95% confidence intervals)

	Total ITT population	Acute aneurysm	Elective aneurysm	Gastrointestinal oncology
No of patients	1051 (526; 525)	79 (35; 44)	412 (207; 205)	560 (284; 276)
Mortality				
No of patients	98 (54; 44)	28 (11; 17)	36 (20; 16)	34 (23; 11)
Odds ratio	0.80 (0.53 to 1.21)	1.37 (0.54 to 3.51)	0.79 (0.40 to 1.57)	0.47* (0.23 to 0.99)
Intensive care unit stay†				
Mean (days)	4.3 (4.5; 4.1)	12.2 (10.5; 13.6)	4.7 (5.3; 4.1)	2.9 (3.1; 2.7)
Difference	−0.4 (−1.63 to 0.61)	3.0 (−3.5 to 9.6)	−1.2 (−2.88 to 0.40)	−0.5 (−1.33 to 1.00)
Hospital stay				
Mean (days)	16.8 (17.9; 15.6)	22.2 (22.9; 21.6)	14.3 (15.7; 13.0)	17.8 (19.0; 16.5)
Difference	−2.4* (−4.75 to 0.005)	−1.3 (−10.5 to 7.9)	−2.7 (−5.7 to 0.3)	−2.4 (−6.1 to 1.2)
Multiorgan failure‡				
No of patients	164 (91; 73)	43 (19; 24)	74 (42; 32)	47 (30; 17)
Odds ratio	0.70* (0.49 to 0.999)	1.01 (0.41 to 2.46)	0.73 (0.44 to 1.21)	0.56 (0.30 to 1.03)
Infection§				
No of patients	244 (121; 123)	34 (15; 19)	77 (41; 36)	133 (65; 68)
Odds ratio	0.98 (0.73 to 1.32)	0.95 (0.38 to 2.37)	0.86 (0.52 to 1.42)	1.07 (0.73 to 1.59)

*P≤0.05.
†n=1042; data missing for nine patients.
‡n=1034; data missing for 17 patients.
§n=1011; data missing for 40 patients.

Hospital stay—Patients randomised to filtered products stayed an average of 2.4 days less (4.8 to 0.0 day). The figure shows the length of stay in the total population and in those patients undergoing elective surgery for aneurysm.

Discussion

We hoped to provide decision makers with evidence regarding a universal leucocyte filtration programme. The study ended early because politicians decided to mandate universal leucocyte filtration of red blood cells in the Netherlands to reduce the risk of transmission of prions through non-filtered transfusions. However, this meant that we had to stop recruitment before we reached our planned study size.

Interpretation and context

We found no significant differences in the primary end points (mortality and stay in intensive care). With respect to secondary end points, we found a significant difference in the incidence of postoperative multiorgan failure in favour of filtered products. The incidences of postoperative infections were not significantly different between the two randomised groups. The mean hospital stay was 2.4 days shorter in the group randomised to filtered products.

Although we found no significant benefit of filtered products on mortality in hospital in the total population, we did see an effect in the subgroup of patients undergoing gastrointestinal surgery. We excluded an apparent imbalance in randomisation (which could have caused this difference) by showing that with respect to relevant risk factors the distribution of randomised gastrointestinal patient to non-filtered and filtered products was balanced (see bmj.com). This observation is in agreement with the outcomes of a recent randomised controlled trial in cardiac surgery[10] and of the Canadian registration study.[11]

We found no evidence to support the use of filtered products to prevent infection in patients undergoing major surgery. In our three previous studies that compared filtered products with red blood cells with the buffy coat removed (the standard Dutch product), we found a reduction in postoperative infections only in patients undergoing cardiac surgery who had received more than 3 units.[6 10 12] Others reported a correlation between the number of blood transfusions and multiorgan failure.[12] In our previous (multicentre) non-cardiac surgery study[6] and in the present study only a relatively small number of patients received 4 or more units.

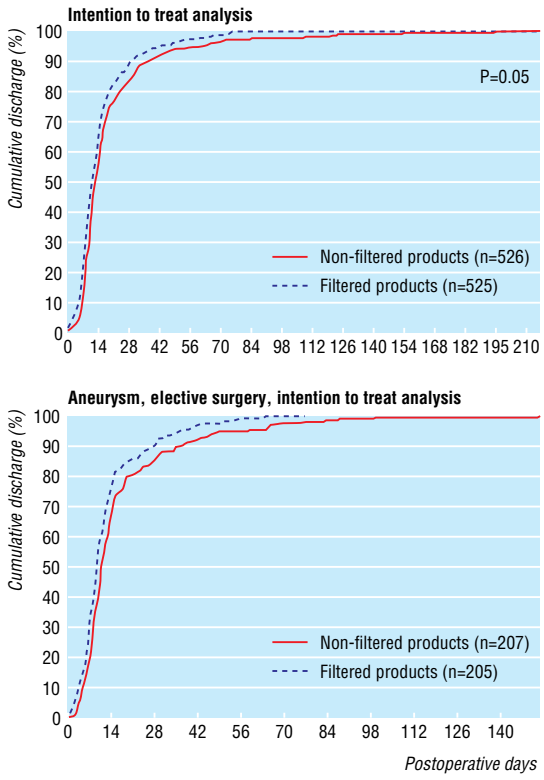
Economic evaluation

Another benefit of filtered products in our study, besides a reduced incidence of multiorgan failure, was a reduction in mean length of hospital stay. The reduction in hospital stay was partly due to fewer patients who received filtered products who stayed for more than 90 days in hospital (10 non-filtered *v* 1 filtered). The reduction in hospital stay was present in all subgroups and most pronounced in the patients undergoing elective surgery for aneurysm who received transfusions. The two Canadian intervention studies also showed a reduction in hospital stay.[11 13] Reduction in hospital stay supports the general leucocyte reduction of red blood cells by filtration. If we extrapolate the benefit of filtrated products to the

Table 3 Patients undergoing gastrointestinal surgery differentiated by sex, age, type of surgery, blood transfusion with filtered or non-filtered red blood cells, and duration of surgery according to survival

		Survived		Died†	
	Total* (n=560)	Non-filtered (n=284)	Filtered (n=276)	Non-filtered (n=23)	Filtered (n=11)
Sex:					
Male	318	167	151	12	9
Female	242	117	125	11	2
Age (years):					
<60	174	88	86	5	2
60-70	179	90	89	5	5
>70	207	106	101	13	4
Units of red blood cells transfused:					
0	303	147	156	5	3
1-3	137	75	62	6	1
4-10	90	44	46	7	3
>10	30	18	12	5	4
Duration of surgery (mins):					
<120	172	81	91	6	3
120-179	162	87	75	9	2
180-239	115	59	56	3	2
240-359	76	37	39	4	4
≥360	35	20	15	1	0
Type of surgery:					
Upper GI surgery‡	131	60	71	6	5
Laparotomy	26	16	10	2	1
Colectomy	118	64	54	5	1
Rectal (sigmoid) resections	285	144	141	10	4

*Equal distributions.
†Unequal distributions between non-filtered and filtered products.
‡Includes resections of oesophagus, gastrectomy, liver surgery, jejunectomy, pancreatico-duodenectomy.



Cumulative hospital discharges

What is already known on this topic

Reduction of leucocytes in red blood cell concentrates by filtration results in less alloimmunisation in patients receiving transfusions and transplants

In patients undergoing cardiac surgery and transfused with at least 4 units the use of filtered red blood cells reduces postoperative infections and mortality

The use of filtered red blood cells has also been shown to reduce postoperative infections in patients undergoing colorectal surgery

What this study adds

The use of filtered red blood cells results in a shorter stay in hospital and a lower incidence of multiorgan failure in patients undergoing major vascular or oncological surgery

Mortality was lower in the subgroup of patients undergoing gastrointestinal oncological surgery

Dutch healthcare system, with 16 300 aneurysm and gastrointestinal procedures a year, a mean reduction of 2.4 days in hospital would reduce the national hospital costs by €29.5m/year (£19.6m, $35.0m). In the Netherlands the annual cost of universal leucocyte depletion of red blood cells is about €20m (assuming filtration costs of €40/unit). The reduced mean hospital stay associated with filtered products could, to a large extent, compensate the extra cost of filtration in the Netherlands. In other countries where standard whole blood transfusion has been compared with filtered red blood cells, implementation of filtration seems to be cost neutral or cost saving in some settings.[14 15]

Conclusions

Although we had to stop recruiting patients before we reached the desired study size, results for some end points had reached significance. Leucocyte reduced transfusions in this group of patients undergoing major surgery significantly reduced the incidence of multiorgan failure and length of hospital stay. Our results also contribute to the discussion of the cost effectiveness of using filtered red blood cells.

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Contributors: See bmj.com

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Competing interests: None declared.

Ethical approval: The protocol was first approved by the ethics committee of the Medical Spectrum Twente recognised by Dutch Central Council for Medical Research (CCMO) and subsequently endorsed by all ethics committees of the other participating hospitals.

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Corrections and clarifications

Alcohol limit for drink driving should be much lower
We inadvertently introduced confusion over the blood alcohol concentrations in this letter by Ediriweera B R Desapriya (10 April, p 895). Near the start of the second paragraph, the range should be 0.8 mg/ml to 1.0 mg/ml. The legal limit cited later in that paragraph is 0.8 mg/ml, and the risk of a crash increases above a concentration of 0.2 mg/ml. In the final paragraph, the concentration should again have been cited in mg/ml (as 0.8 mg/ml).

UK academy wants neuroscience research to benefit patients more quickly
In this News Extra article on bmj.com by Chibuzo Odigwe, we wrongly referred to Ray Tallis as the president of the Academy of Medical Sciences (http://bmj.bmjjournals.com/cgi/content/full/328/7443/790-a). He is in fact the secretary of the academy's working group that produced the neuroscience report that was discussed in the article.

Patient power?
An editing slip in this Personal View by Frank Arnold last year (*BMJ* 2003;326:1042) reveals an apparent ignorance on our part of the difference between anal and oral orifices. In the second sentence of the second paragraph we should have expanded the author's original term ("barium") to "barium enema" (not "barium meal").