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ORIGINAL PAPER

Post-transfusion mortality among recipients of ABO-compatible but non-identical plasma

A. Shanwell,[1] T. M.-L. Andersson,[2] K. Rostgaard,[3] G. Edgren,[2] H. Hjalgrim,[3] R. Norda,[4] M. Melbye,[3] O. Nyrén[2] & M. Reilly[2]

[1]*Transfusion Medicine, Karolinska University Hospital, Stockholm, Sweden*
[2]*Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[3]*Statens Serum Institut, Copenhagen, Denmark*
[4]*Akademiska Sjukhuset, Uppsala, Sweden*

Vox Sanguinis

Background and Objectives The consequences of ABO-compatible non-identical plasma for patient outcome have not been studied in randomized clinical trials or large cohort studies and use varies widely in the absence of evidence-based policies. We investigated if transfusion with compatible instead of identical plasma confers any short-term survival disadvantage on the recipients.

Materials and Methods The cohort of all 86 082 Swedish patients who received their first plasma transfusion between 1990 and 2002 was followed for 14 days and the risk of death in patients exposed to compatible non-identical plasma compared to recipients of only identical plasma.

Results After adjustment for potential confounding factors, there was an increased mortality associated with exposure to ABO-compatible non-identical plasma, with the excess risk mostly confined to those receiving 5 or more units (relative risk, 1·15; 95% confidence interval, 1·02–1·29). Stratification by blood group indicated higher risks in group O recipients, especially when the compatible plasma was from a group AB donor.

Conclusions This study suggests that ABO-compatible non-identical plasma is less safe than identical plasma. Subanalyses by blood group suggest a role for circulating immune complexes. Our findings may have policy implications for improving transfusion safety.

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Introduction

Improved donor selection and testing in recent years has led to an unprecedented level of safety of the blood supply [1] and a call for a shift of emphasis from blood safety to transfusion safety [2]. One aspect of transfusion safety concerns the ABO blood groups [3,4] of the donor and recipient. Transfusion of ABO-incompatible red blood cells (RBCs) or plasma is avoided, because it can cause haemolysis and is burdened with high mortality [5–9]. Plasma naturally contains anti-A and/or anti-B antibodies directed against the blood group antigen(s) that are absent in that individual. It is considered safe to use non-identical plasma that has no antibodies against blood group antigen(s) present in the recipient, and plasma from donors with blood group AB (universal plasma) is administered to recipients of all blood groups (see Fig. 1). In addition to its use in emergency cases where the patient's blood type is unknown or when there is a shortage of plasma of the recipient's blood type, some hospital blood banks may issue AB plasma routinely for logistical reasons. The consequences

Correspondence: Marie Reilly, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, 17177 Stockholm, Sweden
E-mail: marie.reilly@ki.se

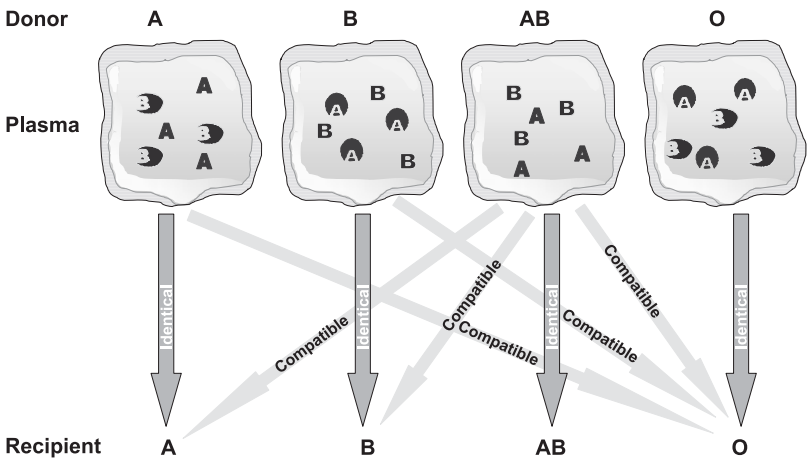

Fig. 1 Definitions of ABO-identical and ABO-compatible non-identical plasma. In addition to soluble blood group antigens (A or B), plasma contains naturally occurring antibodies to the antigen(s) that are lacking (= anti-A antibodies; = anti-B antibodies). Based on the presence or absence of antibodies, plasma for transfusion is chosen as indicated by the arrows (ABO identical plasma or ABO compatible, non-identical plasma).

of using compatible non-identical plasma for patient outcome have not been studied in randomized clinical trials or large cohort studies. An increased morbidity and mortality has been reported in numerous studies of ABO-mismatched platelet concentrates [10–13] and one study that failed to show any adverse effect employed an unorthodox study design, comparing patients based on whether their first transfusion was identical or non-identical, with consequent inevitable misclassification of exposure [14]. However, there is a marked paucity of objective data regarding the use of plasma, and ABO-compatible non-identical plasma may not be harmless. When ABO-compatible non-identical plasma is transfused, the soluble A and/or B antigens may form circulating immune complex (CIC) with the recipients anti-A and/or anti-B antibodies [15], as has been documented for platelet recipients after transfusion of incompatible ABO antibody or antigen [16]. Circulating immune complexes have been shown to be associated with various immunological reactions [17,18].

Our objective was to investigate the effect of ABO-compatible non-identical plasma transfusions on post-transfusion short-term mortality. Since such plasma (especially AB plasma) is frequently used, the consequence of this common practice is a potentially important issue for medicine. The availability of the Scandinavian Donations and Transfusions (SCANDAT) database [19] provides a unique opportunity to examine the post-transfusion mortality in a very large patient population.

Materials and methods

Scandinavian Donations and Transfusions database

The SCANDAT database [19] is a blood donation and transfusion register containing detailed information on approximately 1·3 million transfusion recipients and 1·1 million blood donors. Using unique national registration numbers, individual characteristics and health outcome data were obtained by record linkage with national population, death and hospital discharge registers. The Stockholm Regional Ethics Committee approved the use of these data resources for the study presented here.

Definition of the cohort

From the SCANDAT database, we selected patients for a retrospective cohort study. We included all those with valid national registration numbers, and known date of birth, blood group and transfusion dates, who had their first recorded allogeneic plasma transfusion between 1 January 1990 and 31 December 2002, and who were 18 years or older at the time of this transfusion. We excluded plasma recipients whose first allogeneic plasma transfusion was ABO incompatible or from a donor with unknown blood group. In addition, we excluded all patients who (i) had any history of organ or haematopoetic stem cell transplantation on or prior to the date of first allogeneic plasma transfusion, (ii) received any blood component except autologous plasma or ABO-identical RBCs in the 30 days prior to the first allogeneic plasma transfusion, (iii) on the day of the first plasma transfusion were not recorded at any hospital or were recorded at more than one hospital, or (iv) had blood group AB (since exposure to compatible non-identical plasma is not possible). Hospitals that accounted for fewer than 1000 persons in follow-up were excluded from analysis (thereby restricting the analysis to Swedish hospitals) in order to facilitate investigation of whether different hospital practices had any effect.

Plasma

In Sweden, plasma is mostly derived from buffy-coat-depleted whole blood with the top-and-bottom method [20] and contains less than 6×10^9 erythrocytes/l, which is in accordance with Swedish guidelines. In addition, most plasma is re-centrifuged

and contains less than $0{\cdot}05 \times 10^9$ erythrocytes/l (approximately 0·001% of the erythrocyte concentration in whole blood). Most of the plasma units (95·9%) for the transfusions in this study were prepared from 450 ml whole blood with a small number (4·1%) prepared by apheresis, and the volume of one plasma unit is approximately 270 ml including the anti-coagulant citrate solution.

Statistical analysis

Exposure was defined as being administered a transfusion with ABO-compatible non-identical plasma, and the reference group consisted of recipients who were transfused with only ABO-identical plasma. For each day of follow-up, we modelled the effect on mortality of the total number of RBC units and plasma units received by the patient from the start of plasma transfusion up to and including the previous day. Thus, follow-up began on the day after the first plasma transfusion and patients who had less than 1 day of follow-up contributed no follow-up and were excluded from the main cohort. Exposure was examined as a dichotomous variable (any vs. none) and was also categorized by the number of units of compatible non-identical plasma received (0, 1, 2, 3–4 and 5+). The recipients were followed up for 14 days, until death, or 31 December 2002, whichever came first, and were censored if they received any organ or stem-cell transplant, or any blood component other than ABO-identical RBCs or ABO-identical or compatible non-identical plasma.

Poisson regression was used to estimate relative risk (RR) in exposed patients, with adjustment for the following potential confounding factors: calendar year at start of follow-up, hospital, sex, age at start of follow-up (18–20, 21–25, 26–30 ... 85–90, ≥ 91 years), blood group, indication for transfusion, number of RBC units transfused (0, 1–2, 3–4, 5–9 and 10+), total number of plasma transfusions and time since start of follow-up in days. With the exception of total number of plasma transfusions, the log of which was modelled as a linear covariate, all these were treated as categorical variables. The indication for transfusion was defined from the diagnosis and procedure codes (using the ICD-9 and ICD-10 coding systems) from the hospitalization episode during which the patient entered the cohort, and were grouped into the following six categories: burns, other trauma, non-trauma major cardiovascular surgery, non-trauma non-cardiovascular major surgery for malignant disease, non-trauma non-cardiovascular non-malignancy major surgery and non-trauma care (non-surgical or with minor surgery). To assess possible effects of changing practice in the use of compatible non-identical plasma over time, we also tested for an interaction between hospital and calendar time.

We repeated our analyses stratified by blood group O vs. non-O, and for the group O recipients conducted an analysis where exposure to AB plasma (two antigen plasma) and to A or B plasma (one antigen plasma) were modelled as separate effects. In supplementary analyses, patients who died on the first day of transfusion (and who were thus excluded from the main cohort analysis) were compared to those who survived using a logistic regression model that adjusted for all the same factors as above, with the exception of time. For all risk estimates, 95% confidence intervals (CIs) are provided. Data processing and statistical analyses were performed using SAS version 8 or higher (SAS Institute, Cary, NC, USA).

Results

A total of 165 369 recipients met the inclusion criteria. From these, we excluded 1455 subjects whose first allogeneic plasma transfusion was ABO incompatible or from a donor with unknown blood group, 1556 recipients who had a history of organ or stem cell transplant, 8075 recipients who received blood components other than autologous plasma or ABO-identical RBCs in the 30 days prior to their first allogenic plasma transfusion, 12 003 recipients who were patients at unknown or multiple hospitals, and 6532 recipients who were blood group AB. A further 23 420 recipients did not contribute any follow-up and were therefore excluded from the main cohort. Finally, on restricting to hospitals that accounted for at least 1000 persons in follow-up, the study cohort consisted of 86 082 recipients from 29 Swedish hospitals who were followed for 1–14 days after their first plasma transfusion.

The cohort of recipients is described in Table 1a. A majority (76%) of these recipients had no exposure to any compatible non-identical plasma. The average age was 70 years with slightly more men than women (55% vs. 45%), which is in agreement with other studies [21]. The median year of first plasma transfusion was 1998. The overall distribution of blood group in the cohort reflected the blood group distribution of all Swedish transfusion recipients in the SCANDAT database when blood group AB is excluded (O, 40%; A, 48%; and B, 12%), but as might be expected, the blood group distribution differed markedly between recipients who were exposed to compatible non-identical plasma and those who only received identical plasma; the majority of exposed patients (64%) were of blood group O.

Patients received between 0 and 76 ABO-identical RBC units (average 3·99) during follow-up. Subjects exposed to compatible non-identical plasma received significantly more RBC units (average 4·75 vs. 3·76, $P < 0{\cdot}0001$) and more plasma units (average 5·54 vs. 3·95, $P < 0{\cdot}0001$) during follow-up than did those who only received identical plasma. The 14-day mortality was slightly higher (8·99% vs. 8·14%) in the exposed group. Of the 20 320 exposed recipients, approximately two-thirds (13 142) received only ABO-compatible non-identical plasma, while one-third also received identical plasma (Table 1b). Exposed subjects who received both identical and

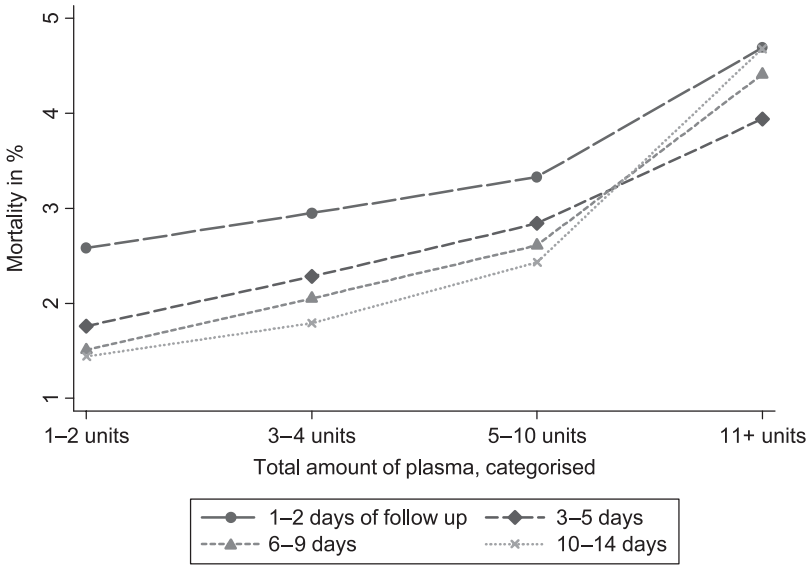

Fig. 2 Fourteen-day mortality of plasma transfusion recipients, stratified by time since first transfusion and number of plasma units received up until that time.

Table 1a Description of the patients included in the study

	Unexposed	Exposed[a]	Total
Number (%) of recipients	65 762 (76%)	20 320 (24%)	86 082
Age, median (min–max)	70 (18–105)	69 (18–100)	70 (18–105)
Sex, M/F %	54·9/45·1	57·3/42·7	55·4/44·6
Year of first plasma transfusion, median (min–max)	1997 (1990–2002)	1998 (1990–2002)	1998 (1990–2002)
Blood group O	33·6%	64·2%	40·8%
Blood group A	57·2%	23·0%	49·1%
Blood group B	9·2%	12·8%	10·1%
Number of RBC units transfused, mean (min–max)	3·76 (0–76)	4·75 (0–59)	3·99 (0–76)
Number of plasma units transfused, mean (min–max)	3·95 (1–147)	5·54 (1–318)	4·33 (1–318)
14-day mortality	8·14%	8·99%	8·34%

[a]Exposed patients are those who received any non-identical plasma.

Table 1b Description of subjects who received non-identical plasma, stratified by whether or not any identical plasma was also given

	Only ABO non-identical plasma	A mixture of ABO-identical and non-identical plasma
Number of plasma recipients	13 142	7178
RBC units transfused, mean (min–max)	3·68 (0–59)	6·71 (0–56)
Plasma units transfused, mean (min–max)	3·21 (1–124)	9·82 (2–318)
14-day mortality	8·35%	10·16%

compatible non-identical plasma received more RBC and plasma transfusions, and had a higher mortality (10·16% vs. 8·35%).

The total number of plasma transfusions (i.e. identical plus non-identical) is an important potential confounder, since this number is linked to the probability of exposure to compatible non-identical plasma, and likely to be associated with mortality through the critical state of the patient needing a larger number of transfusions. Our data suggested such a relationship, as for a given follow-up time, we found a clear trend of increased mortality with larger numbers of transfusions (see Fig. 2). Hospital is another potential confounding factor, since it may be associated with exposure through different hospital transfusion policies, and associated with mortality through case-mix. There were 29 hospitals included in the

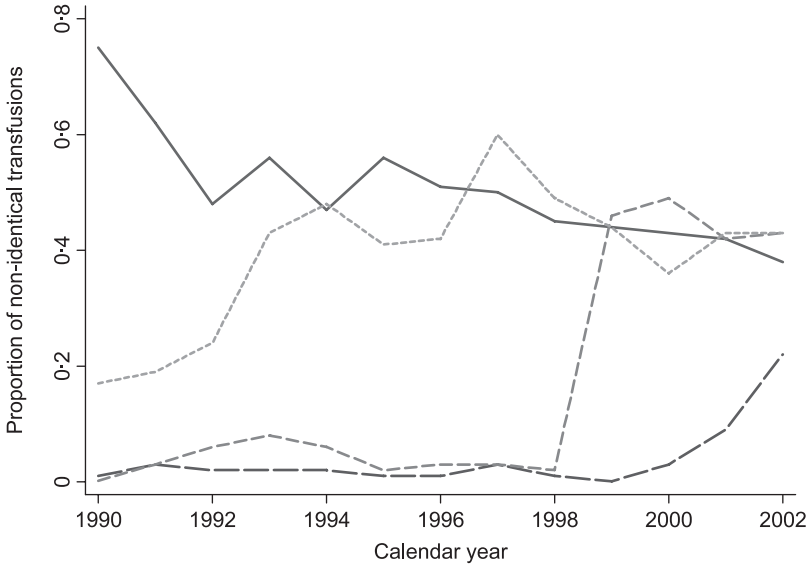

Fig. 3 The proportion of plasma transfusions using non-identical components for four of the largest hospitals over the calendar period of the study.

Table 2 Estimates of relative risk of mortality after transfusion with non-identical plasma from Poisson regression analysis

	Whole cohort		Group O		Group A or B	
Risk factor	**RR[ab] (95% CI)**	***P***	**RR[a] (95% CI)**	***P***	**RR[a] (95% CI)**	***P***
Any exposure to non-identical plasma	1·06 (0·997, 1·13)	0·06	1·16 (1·05, 1·28)	0·004	1·04 (0·95,1·14)	0·39
Number of units of non-identical plasma						
0 (ref)	1·0		1·0		1·0	
1	1·07 (0·95, 1·20)	0·25	1·15 (0·97, 1·36)	0·12	1·06 (0·91, 1·24)	0·46
2	1·05 (0·96, 1·14)	0·30	1·13 (1·00, 1·28)	0·05	1·04 (0·91, 1·18)	0·56
3–4	1·02 (0·91, 1·14)	0·74	1·13 (0·97, 1·32)	0·11	0·97 (0·81, 1·16)	0·72
5+	1·15 (1·02, 1·29)	0·02	1·26 (1·08, 1·47)	0·004	1·12 (0·91, 1·39)	0·29

[a]RR, relative risk adjusted for age, sex, year of transfusion, hospital, indication for transfusion, and total number of plasma and RBC units. Patients receiving only identical units are the reference group. 95% CI, 95% confidence interval.

[b]Adjusted for blood group (A, B and O).

study, and for four of the largest hospitals, Fig. 3 presents the proportion of plasma transfusions that used ABO non-identical plasma in different calendar years. It is clear from this figure that some hospital blood banks had apparent shifts in policy while in others there was a gradual change over time. Thus, the effects of hospital, calendar time and the interaction between these two factors were considered during model selection.

The results from the multivariate Poisson regression analyses of the whole cohort are presented in Table 2. Compared to recipients of identical plasma only, there is a trend for increased mortality associated with any exposure to compatible non-identical plasma after adjustment for the potential confounding factors listed earlier (RR, 1·06; 95% CI, 0·997–1·13; *P*-value, 0·06). On examination of the dose–response, there is a raised risk for all levels of exposure, but only 5 or more units of compatible but non-identical plasma are associated with a significantly increased mortality (RR, 1·15; 95% CI, 1·02–1·29). We also compared those recipients who died on the first day to those who survived, and observed an increased mortality for those who received 3 or more units of compatible but non-identical plasma on the first day (3–4 units: RR = 1·26, 95% CI = 1·01–1·56; 5+ units: RR = 1·33, 95% CI = 1·06–1·67). As expected, we found significant interactions between hospital and calendar time, but these did not substantially modify the estimated risks associated with compatible non-identical plasma (data not shown).

Recipients with different blood groups may have a different response to non-identical plasma due to variations in antibody levels and specificity by blood group [22,23]. To investigate whether such differences were apparent in our data, we repeated our analyses stratified by blood group O vs. A or B, and the results are presented in Table 2. From our analysis in the total cohort, we found an overall increased risk among

Table 3 Relative risk of death in group O recipients after transfusion with A, B and AB plasma

	AB plasma			A or B plasma		
Risk factor	***n***	**RR (95% CI)**	***P***	***n***	**RR (95% CI)**	***P***
Ever exposed to compatible non-identical plasma of the type(s) specified	481	1·20 (1·07, 1·33)	0·001	868	1·06 (0·96, 1·18)	0·26
Number of units						
0 (ref)	2512	1·0		2125	1·0	
1	124	1·22 (1·01, 1·46)	0·04	111	0·94 (0·76, 1·15)	0·52
2	196	1·13 (0·97, 1·31)	0·12	322	1·07 (0·93, 1·23)	0·32
3–4	105	1·47 (1·20, 1·80)	0·0002	188	1·04 (0·88, 1·23)	0·64
5+	56	1·02 (0·77, 1·35)	0·89	247	1·17 (0·99, 1·38)	0·07

n, number of deaths; RR, relative risk adjusted for age, sex, year of transfusion, hospital, indication for transfusion, and total number of RBC and plasma units. 95% CI, 95% confidence interval.

exposed blood group O patients relative to group O patients who received only identical plasma (RR, 1·16; 95% CI, 1·05–1·28). There was no obvious trend of increasing risk with increasing number of compatible non-identical plasma transfusions, although as before, the highest and most significant risk was for patients receiving 5 or more units (RR, 1·26; 95% CI, 1·08–1·47). The corresponding overall RR among patients of blood group A or B tended to be lower (RR, 1·04; 95% CI 0·95–1·14), with no statistically significant risk for any dose.

Restricting our analysis to recipients with blood group O, we estimated the RR of death associated with exposure to non-identical plasma from donors of different blood types. Table 3 presents the adjusted RR estimates for exposure to AB plasma and to A or B plasma. Blood group O recipients who received compatible non-identical AB plasma had a significantly higher risk than group O recipients who received only identical plasma (RR = 1·20; 95% CI = 1·07–1·33), whereas there was no significant risk to blood group O recipients of A or B plasma (RR = 1·06; 95% CI = 0·96–1·18). There was no clear dose-risk trend with number of compatible non-identical plasma transfusions, although the risk estimates were highest for group O recipients of 3–4 units of compatible non-identical AB plasma (RR = 1·47; 95% CI = 1·20–1·80) and 5+ units of compatible non-identical A or B plasma 1·17 (0·99, 1·38). In addition, group O recipients exposed to even a single unit of AB plasma have a significantly increased mortality (RR = 1·22; 95% CI = 1·01–1·46), while an increased risk for A or B plasma is only apparent for the largest dose (5 units or more) and even then does not achieve statistical significance.

Discussion

In this retrospective cohort study based on the SCANDAT database, transfusion of ABO-compatible non-identical plasma was associated with a significantly increased 14-day post-transfusion mortality. The overall risk was most apparent for those who had received the largest amounts of compatible non-identical plasma. In support of our *a priori* hypothesis that soluble blood group antigens in the transfused compatible but non-identical plasma might react with the recipients' anti-A or anti-B antibodies, we observed a slightly higher RR of dying within 14 days among recipients who were blood group O (who have higher titre and greater avidity anti-A and anti-B antibodies than have recipients with other blood groups [23]), and among the latter, in those who had received AB plasma (which contains greater quantities of blood group antigens than does A or B plasma).

It has been documented that transfusion of incompatible ABO antibody or soluble antigen leads to the accumulation of CICs in the recipient's peripheral blood [16]. The slightly higher risk among recipients with blood group O, and particularly among those who received AB plasma, provides indirect support for the hypothesis that CICs are responsible for the increased mortality with ABO non-identical plasma [17,18]. Residual RBC stroma could also be involved in the CIC mechanism, as such RBC contamination would add to the amount of ABO antigen in the ABO-compatible non-identical units. However, with the top-and-bottom preparation and re-centrifugation step, such contamination is likely to be too small (compared to the soluble antigen) to be of concern in this study.

The adjusted RR of 1·06 among our recipients exposed to ABO-compatible but non-identical plasma may seem trivial, but with an observed 14-day mortality of 8·99%, this RR corresponds to a risk difference of 0·51%, or one extra death per 195 patients transfused with compatible but non-identical plasma over a 14-day transfusion 'episode' [24]. Although the strength of the association might have been overestimated due to residual confounding by indication, this is much higher for example than the rate of transfusion related acute

lung injury that has led to the exclusion of plasma from female donors in several countries [25,26].

The major strengths of this study are the large sample size that enabled analysis of mortality ratios by exposure dose and in detailed subanalyses stratified by characteristics of the recipients, follow-up without losses through complete population and death registers, and data that represent the entire transfusion experience in two developed countries, ensuring external validity. The limitations include the paucity of individual information on potential confounding factors, that is, factors that are determinants of the risk of dying and that might be unevenly distributed among exposed and unexposed patients. Confounding by unmeasured cofactors might well explain associations of the order of magnitude observed in our study. In particular, confounding by underlying disease severity (which could be the result of selection bias into the exposed subcohort) is a serious concern. On the one hand, the choice of the ABO blood group of plasma transfused in Sweden is not made by the patients' physicians but by the blood centre or blood bank, without knowledge of the clinical state of the patient for whom the blood component is intended. Hence, the choice of blood component will be primarily influenced by the hospital or blood bank's policy (concerning ABO match) and the availability of plasma. This would likely weaken any links between the severity of the patient's condition and the exposure. On the other hand, it is conceivable, in a hospital with a policy to use only identical plasma, that a desperate clinical situation forces the clinician and/or the blood bank to temporarily relinquish this policy, either due to the urgency or because the stores of identical plasma have been depleted.

We have taken various measures to minimize confounding by disease severity. Our estimates were adjusted for indication in broad categories, and for total numbers of RBC and plasma units, which, as expected, were strongly related to mortality. Additionally, we adjusted for sex, age, and blood group, as well as for calendar year and hospital, since confounding could result from hospital policy regarding allocation of identical or non-identical plasma. Conceivably, the estimated effects of exposure to non-identical plasma could be due to confounding by being mainly present in a population of recipients whose greater need of blood results in them being exposed to a mixture of identical and non-identical plasma. This is suggested by the similar crude survival of the unexposed recipients and those receiving only non-identical plasma (Table 1). However, in a nested case–control study in a cohort restricted to patients who received only identical or only compatible plasma, we found the effect estimates for exposure to be consistent with those obtained from the whole cohort, suggesting that such confounding has been controlled. We have also considered the possibility that some of the exposed patients do not just need more blood, but need it quickly, so that the compatible plasma is given in an emergency situation. This would again lead to confounding, as these patients are likely to have higher risk of death. To assess the potential for such confounding, we compared the mortality in the unexposed recipients in our cohort and the AB recipients (who were excluded from our main cohort) who received only identical plasma, adjusting for all the same factors as before, and found no significant difference in the risk for AB vs. non-AB recipients. This suggests a sufficient control of confounding due to emergency indications in our main analysis, since the same proportion of AB patients will have been administered AB plasma without knowledge of their blood group as among the other patient groups.

The excess risk we detected for compatible but non-identical plasma, although small, is sufficiently high to have an important impact on the population level. However, despite our efforts to minimize confounding, this is an observational study where it is possible that there are non-causal explanations for our findings, such as residual confounding from unmeasured factors. Nonetheless, we find it difficult to dismiss the observed excess mortality. We do not believe that a larger observational study is feasible in the foreseeable future, or indeed that such a study will be much more informative as it will be subject to the same uncertainty regarding confounding. Rather, a large-scale randomized clinical trial seems to be warranted in order to confirm the safety level of compatible but non-identical plasma. In conclusion, our results provide an important body of evidence relevant to this little-studied clinical question, suggesting that the concept of 'universal plasma' should be re-examined and whenever possible, ABO-identical plasma should be used as the first choice.

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