Transition from fresh frozen plasma to solvent/detergent plasma in the Netherlands: comparing clinical use and transfusion reaction risks

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Protocol/hospital details:
Study approved by medical ethical committee of the Leiden University Medical Centre (protocol number P13.251) and funded by a grant from Sanquin (PPOC-13-RvB-04). The protocol was reviewed and approved by representatives at each hospital, three academic hospitals (Leiden University Medical Centre; Maastricht University Medical Centre; University Medical Centre Utrecht) and three general hospitals (Maasstad hospital, Rotterdam; Isala hospital, Zwolle; OLVG location East, Amsterdam).

Data sources information
National blood bank data: For the analysis of blood product use at the national level, we chose units issued as our parameter as this represents the true national demand for plasma. From Sanquin Blood Bank we collected the number and type (i.e.: FFP or SD plasma) of plasma units distributed to each of the 94 Dutch hospitals during the period 2012-2017, along with hospital type (academic medical centre or general hospital).

Hospital data: From each of the six participating hospitals, we collected the following data on all blood products transfused for transfusion episodes involving plasma transfusion during all or part of the period 2010-2016: coded patient ID; patient sex; patient year of birth; diagnostic code and associated treatment description described using codes as defined by the Dutch healthcare authority[1]; treating ward; transfusion start and end times; type and unique Unit Identification Number of the blood product transfused.

Hemovigilance data: From TRIP, the Dutch national hemovigilance and biovigilance office, we collected the number and type of transfusion reactions reported by all Dutch hospitals, along with the potentially associated blood products as provided by the reporting hospitals. Each transfusion reaction reported to TRIP is reported with an imputability of 'certain', 'probable', 'possible', 'unlikely', or 'certainly not', describing the certainty with which the transfusion reaction can be attributed to the transfused blood product[2]; here we analysed data on reactions with imputability levels of 'certain', 'probable', and 'possible'.

Ward hierarchy details
As each transfusion was coded with multiple diagnostic codes, often from different wards, we assigned each transfusion episode to only one ward with a hierarchy of cardiothoracic surgery + cardiology > general surgery > gynaecology > other. This ensured each episode was analysed in one ward group, and potentially one diagnosis group. These four ward groups (cardiothoracic surgery + cardiology; general surgery; gynaecology; other) and the four diagnosis groups (CABG+VR+maze; aneurysm; obstetric; TTP/HUS) were used throughout the analysis.

For our second sensitivity analysis, the modified hierarchies used were (1) general surgery > cardiothoracic surgery + cardiology > gynaecology > other and (2) gynaecology > general surgery > cardiothoracic surgery + cardiology > other.

Patient exclusions
For our Patient-level blood product use analysis, we excluded the TTP/HUS group as plasma-exchange for TTP/HUS does not typically involve RBC transfusion and the plasma is not given to stop bleeding. We

used bootstrapping with 10,000 iterations to model distributions for these three means for SD plasma and FFP and calculated mean differences and 95% confidence intervals using a two-tailed t-test on the bootstrap estimates assuming unequal variance.

Some plasma exchange patients with diagnoses other than TTP/HUS (who are thus not excluded from analysis) received a unit of red blood cells within 72 hours of a plasma exchange episode. This would then give them an 'active bleeding' status in our analysis of plasma/RBC ratio and units of RBCs transfused in conjunction with plasma. As plasma exchange patients, their plasma/RBC ratio would be enormous as the amount of plasma they receive was aimed at exchange, rather than stoppage of active bleeding. To eliminate these outliers for both SD plasma and FFP, we excluded episodes involving more than 20 units of plasma from our use analysis.

Transfusion Reaction Definitions

Definitions used for these transfusion reactions[2] are a modified version of the International Society of Blood Transfusion (ISBT) Haemovigilance Working Party's *Proposed Standard Definitions for Surveillance of Non Infectious Adverse Transfusion Reactions*[3]. Risk ratios comparing SD plasma and FFP with regard to these transfusion reactions were calculated and tested against the null hypothesis of no difference using Fisher's exact test. The resulting risk ratios (RRs) compare the risks of experiencing the given transfusion reaction for SD plasma vs. FFP (i.e. RR<1 indicates fewer transfusion reactions are associated with SD plasma than FFP).

References

1. Werken met dbc's ziekenhuiszorg. *Nederlandse Zorgautoriteit*. https://werkenmetdbcs.nza.nl/zz-releases/rz18a/menu-ID-3391 (accessed April 4, 2018).
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3. Popovsky M, Robillard P, Schipperus M, Stainsby D, Tissot J-D, Wiersum-Osselton J. Proposed Standard Definitions for Surveillance of Non-Infectious Adverse Transfusion Reactions. *ISBT Working Party on Haemovigilance* 2011;6–9. https://www.isbtweb.org/working-parties/haemovigilance/ (2011, accessed February 4, 2018).

Supplemental Table 1: Mean and mean difference bootstrap 95% confidence intervals for number of plasma units, number of RBC units, and ratio thereof (plasma/RBC units) for each analysis cohort - *episodes involving plasma and RBC transfusion*.

	CT surgery + cardiology		general surgery		gynecology		other	entire cohort
	all	*CABG,VR,maze*	*all*	*aneurysm*	*all*	*labor*	*other*	*entire cohort*
FFP episodes	6,057	2,671	2,536	358	465	337	1,782	10,840
SD plasma episodes	1,831	868	778	131	135	108	326	3,070
mean plasma units per episode:								
mean #FFP units (μ_{FFP})	3.44 (3.36, 3.53)	3.44 (3.32, 3.56)	3.91 (3.78, 4.06)	5.23 (4.82, 5.68)	3.26 (3.00, 3.55)	3.40 (3.10, 3.77)	2.99 (2.86, 3.14)	3.47 (3.41, 3.53)
mean #SD plasma units (μ_{SD})	3.77 (3.61, 3.93)	3.62 (3.43, 3.85)	3.86 (3.63, 4.11)	4.17 (3.72, 4.70)	2.74 (2.45, 3.15)	2.83 (2.48, 3.31)	2.96 (2.70, 3.29)	3.66 (3.54, 3.78)
$\Delta\mu$ ($\mu_{SD} - \mu_{FFP}$)	0.33 (0.15, 0.51)	0.18 (-0.05, 0.42)	-0.06 (-0.34, 0.22)	-1.06 (-1.71, -0.41)	-0.52 (-0.95, -0.08)	-0.56 (-1.09, -0.04)	-0.03 (-0.35, 0.29)	0.19 (0.06, 0.32)
sig.	p<0.01	p=0.13	p=0.69	p<0.01	p=0.02	p=0.04	p=0.87	p=0.01
mean RBC units per episode:								
mean #RBCs (μ_{FFP})	5.27 (5.13, 5.42)	4.97 (4.80, 5.15)	6.79 (6.57, 7.04)	8.68 (8.04, 9.39)	5.32 (4.95, 5.77)	5.19 (4.79, 5.70)	4.90 (4.67, 5.19)	5.57 (5.46, 5.67)
mean #RBCs (μ_{SD})	5.63 (5.40, 5.88)	5.30 (5.02, 5.64)	6.24 (5.89, 6.63)	7.02 (6.27, 7.92)	4.35 (3.93, 4.85)	4.43 (3.93, 5.04)	5.09 (4.63, 5.67)	5.67 (5.49, 5.86)
$\Delta\mu$ ($\mu_{SD} - \mu_{FFP}$)	0.36 (0.08, 0.64)	0.34 (-0.02, 0.69)	-0.55 (-0.98, -0.12)	-1.66 (-2.72, -0.61)	-0.97 (-1.59, -0.35)	-0.76 (-1.47, -0.05)	0.19 (-0.39, 0.78)	0.10 (-0.11, 0.31)
sig.	p=0.01	p=0.06	p=0.01	p<0.01	p<0.01	p=0.04	p=0.53	p=0.35
mean plasma/RBC ratio:								
plasma/RBC (f_{FFP})	0.89 (0.87, 0.91)	0.93 (0.90, 0.96)	0.76 (0.74, 0.80)	0.73 (0.68, 0.79)	0.70 (0.66, 0.76)	0.72 (0.68, 0.77)	0.92 (0.87, 0.98)	0.86 (0.84, 0.88)
plasma/RBC (f_{SD})	0.93 (0.89, 0.97)	0.95 (0.90, 1.01)	0.78 (0.74, 0.83)	0.73 (0.66, 0.85)	0.69 (0.64, 0.75)	0.71 (0.65, 0.78)	0.86 (0.76, 1.06)	0.87 (0.85, 0.91)
Δf ($f_{SD} - f_{FFP}$)	0.03 (-0.01, 0.08)	0.02 (-0.04, 0.08)	0.02 (-0.04, 0.08)	0.00 (-0.11, 0.11)	0.01 (-0.08, 0.06)	-0.01 (-0.09, 0.07)	-0.07 (-0.21, 0.08)	0.01 (-0.02, 0.05)
sig.	p=0.14	p=0.47	p=0.51	p=0.96	p=0.83	p=0.81	p=0.37	p=0.48
mean plasma/RBC ratio (>5 RBCs):								
plasma/RBC (f_{FFP})	0.58 (0.57, 0.60)	0.59 (0.57, 0.61)	0.54 (0.52, 0.56)	0.58 (0.55, 0.63)	0.57 (0.53, 0.62)	0.62 (0.57, 0.68)	0.49 (0.46, 0.52)	0.56 (0.55, 0.57)
plasma/RBC (f_{SD})	0.59 (0.56, 0.62)	0.56 (0.53, 0.60)	0.57 (0.53, 0.60)	0.54 (0.48, 0.59)	0.57 (0.50, 0.64)	0.59 (0.51, 0.67)	0.48 (0.43, 0.53)	0.57 (0.55, 0.59)
Δf ($f_{SD} - f_{FFP}$)	0.01 (-0.03, 0.04)	-0.03 (-0.07, 0.01)	0.03 (-0.01, 0.07)	-0.05 (-0.11, 0.02)	-0.01 (-0.09, 0.08)	-0.03 (-0.13, 0.07)	-0.01 (-0.07, 0.05)	0.02 (-0.01, 0.04)
sig.	p=0.72	p=0.21	p=0.18	p=0.17	p=0.90	p=0.56	p=0.71	p=0.19

Mean differences are calculated as mean$_{SD}$ - mean$_{FFP}$ i.e. a positive value indicates a higher value for SD plasma, and vice versa. Abbreviations: CABG (cardio arterial bypass graft); CT surg. (cardiothoracic surgery); eps (episodes); FFP (fresh frozen plasma); IQR (interquartile range); maze (maze procedure); RBCs (Red Blood Cell units); SD plasma (solvent/detergent treated pooled plasma); sig. (significance)

Supplemental figure 1: f = plasma/RBC units ratio for FFP and SD plasma along with $\Delta f = f_{SD} - f_{FFP}$ for episodes involving ≥5 red blood cells units.
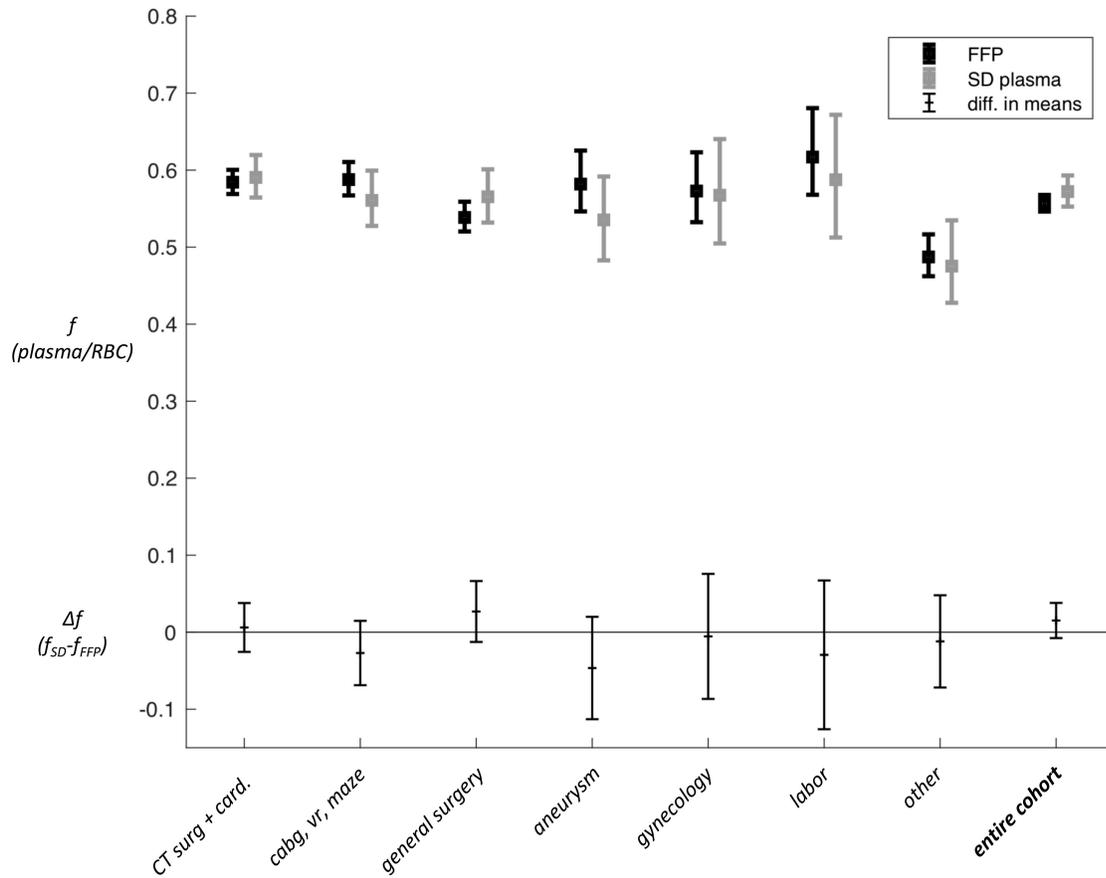
Abbreviations: CABG, VR, maze (coronary artery bypass graft, valve replacement, maze); CT surg + card. (cardiothoracic surgery + cardiology); FFP (fresh frozen plasma); RBC (red blood cell); SD plasma (solvent/detergent treated pooled plasma)