Can we prevent vasovagal reactions in young inexperienced whole blood donors? A placebo controlled study comparing effects of a 330 vs 500 mL water drink prior to donation

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BACKGROUND: Complications of donation reduce donor return. Younger and less experienced donors are more likely to experience vasovagal-type reactions (VVR). A water drink of approximately 500 mL shortly before donation may reduce VVR, but the effect of a smaller volume of water has not been investigated.

STUDY DESIGN AND METHODS: A placebo-controlled comparative study was conducted among donors < 30 years who attended for a 1st-4th whole blood (WB) donation. Collection centers were assigned to offer one of three interventions: 500 mL water drink, 330 mL water drink, or a placebo intervention consisting of pre-donation arm exercise. Within 7 days after attending, participants received an electronic questionnaire about possible symptoms during and after donation. In additional centers, control donors were recruited, who only received standard care and were also sent the questionnaire. Self-reported VVR and other complications were evaluated in all groups.

RESULTS: Out of 8,300 participating donors, 6,921 (83%) returned the questionnaire. Overall, 18.5% of responding donors reported moderate or worse VVR symptoms. In 2nd-4th time donors, both water volumes decreased the odds of a VVR compared to standard care controls (OR_{500ml} 0.75, 95% CI 0.59–0.94; OR_{330ml} 0.73, 0.58–0.91; adjusted combined OR 0.77, 0.64–0.94). There was no effect in new donors or the placebo group compared to controls.

CONCLUSION: In young donors making their 2nd-4th WB donation, drinking water was associated with 23% fewer VVR with no difference between 330 and 500 mL. This decrease was not found in the placebo group. The findings support advocating drinking water for the prevention of VVR.

Blood donor retention increases when a donation is successfully accomplished. Some donors do not return if they experience a vasovagal reaction or other complication of donation.[1–7] Not only do blood establishments have the responsibility to care for their donors' health, they also face the challenge of maintaining an adequate donor base in order to meet needs for transfusion and plasma for plasma-derived medicines. Recruiting young donors is desirable, but young donors are more likely to suffer from complications.[8–10] For these reasons, it is important for blood establishments to ensure that donors will have positive donation experiences and gain confidence in their ability to donate.

The past two decades have witnessed increasing awareness of the impact of donation complications. Research on psychological factors has studied different aspects such as donor motivation, effects of stress, social distraction, and predictive factors for donor return.[1–4,7,11–19] Moreover, risk factors for vasovagal reactions (VVR) have been investigated: reactions are more likely to occur in young donors, women, new or relatively inexperienced donors, and donors with a smaller estimated blood volume (EBV).[8–10,20–25] Factors vary according to the time at which a reaction occurs, with female sex and smaller EBV predicting late reactions. An independent association of VVR with a higher pre-donation hemoglobin level (Hb) has been described but is not yet well understood.[1,26,27]

A number of specific strategies for reducing the occurrence of VVR have been studied, notably applied muscle

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tension, social distraction, drinking water or another fluid a short time before phlebotomy, and deferring young donors with a small EBV.[11,14,28–38] However, the studies are generally not randomized or quasi-randomized, use different outcome measures, and most do not systematically assess compliance with the intervention. The systematic review and meta-analysis by Fisher et al.[30] of interventions to reduce VVR examined the evidence for pre-donation water and found that in five studies, including a total of 12,042 donors, the relative risk of VVR for donors receiving water was 0.79 [95% confidence interval (CI) 0.70–0.89, P < 0.0001] compared to controls. However, after exclusion of trials judged to be at high risk of bias the effect was no longer statistically significant. A subsequent study by Morand et al.[32] has reported similar reductions in donor-reported VVR with water or isotonic fluid with or without applied muscle tension, however the study size was insufficient for it to yield statistically significant results for the separate interventions. All these studies use a relatively large volume of fluid: a pint (US: 473 mL, Imperial: 568 mL) or 500 mL. Apart from a small study of the effects of 300 mL in 93 "high-risk" donors,[35] we are not aware of any studies using a smaller volume. Our study aimed to obtain a comprehensive evaluation of two volumes of water using a post-donation electronic questionnaire. We investigated effects and acceptability of drinking 330 or 500 mL water during the wait (within 15 minutes) before whole blood (WB) donation in younger (up to 30 years old), inexperienced (first, second, third, or fourth donation) donors, comparing this to a control intervention shortly before phlebotomy, and a questionnaire-only condition where standard donor care was given.

METHODS

Study design

The EPISoDe study ("Experience Success in Donation") was designed as a pragmatic controlled intervention study within the Dutch national blood establishment, Sanquin, which provided all funding. The study protocol was approved by Sanquin's ethical advisory board (August 2014).

The study consisted of three conditions initially. The intervention groups consisted of a 500 mL water drink, 330 mL water drink (volumes of the standard bottle sizes), or foam ball squeezing in the waiting area before the phlebotomy started. Foam ball squeezing was intended to be a placebo (control) intervention to achieve a comparable experience for the donor by actively participating in a preventive measure and getting the same level of attention from staff in addressing the possibility of (all types of) complication: it was expected not to have an effect on VVR but to be plausible as an intervention to reduce venipuncture problems. After 7 months a second control group, where only standard care was given, was added as described below. Inclusion in participating clusters started in December 2014 and closed at the end of August 2016.

Participants

Registered donors at Sanquin up to 30 years of age, attending after routine invitation for their first, second, third, or fourth whole blood donation, were eligible to participate in the study. (Note that in the Netherlands all donors first attend for interview and testing on a separate occasion before they are invited for their first donation.) At registration, staff recognized eligible donors from the year of birth and number of donations (both printed on the donation form) and gave them the information sheet describing the study. The name of the study and donor information were designed to chiefly focus on successful collection in order to minimize donor expectation bias but the main target outcome was that of VVR.

Donors then underwent routine health screening according to Sanquin's standard methods. If the donor was eligible for donation they were asked whether they would like to participate in the study and indicated consent by writing their email address on the study form.

Study groups and regions

Collection center clusters in two out of four geographic regions of the country were allocated to apply one of the three interventions. Each cluster (n = 29 nationally, 6–8 per region) consists of at least one fixed center and most include mobile bus locations served by the same collection team. Clusters were assigned to intervention groups sequentially according to their administrative center number, in strata according to geographic region, presence/absence of mobile collections, and presence/absence of a large city (> 100,000 inhabitants). All centers and bus locations within a cluster were assigned to the same intervention. The questionnaire-only control group was recruited in all clusters of a third geographic region.

Procedures

Consenting donors were instructed to drink the water or perform the ball squeezing during the waiting time between screening and blood donation. Donors in the questionnaire-only control group received no extra instructions. At WB donation a standard volume of 500 mL of WB was collected, excluding test samples. Staff were instructed that the study intervention should not influence routine donor care such as advice to eat or to drink extra fluids if the donor was not assigned to the water intervention. A donor could participate once (per intervention or control group).

At blood collection, staff noted on the study form to what extent the donor had finished the bottle of water, and (in the squeezing study arm) the side on which the squeezing and the phlebotomy were performed. Standard blood collection procedures were followed. This included routine recording of

any procedural problems or complications in the blood service information system eProgesa (MAKsystems, Paris).

Electronic questionnaire

Participating donors were sent an email link to an online questionnaire about their donation experience within a week following their donation (see appendix). The questionnaire was designed in Questback Essentials, an online questionnaire platform (Questback, Oslo). One reminder was sent after approximately 2 weeks by email in the event of non-response. The questionnaire was based on the Blood Donor Reactions Inventory (BDRI).[25] Donors rated whether they had symptoms from 11 physiologic reactions (including hematoma) on a five-point scale ranging from 1 = not at all to 5 = to an extreme degree. Responses were included in analyses if they were received within 28 days of the donation.

Study outcome measures

The primary outcome measure was the occurrence of vasovagal complications as measured by the questionnaire responses. We defined a vasovagal-type reaction (VVR, a dichotomous variable) as moderate or worse dizziness and/or nausea and/or fainting as reported by the donor in the questionnaire. Secondary outcome measures from the questionnaire responses were fatigue, delayed VVR (reactions which occurred after the donor had left the collection center), and other complications.

An additional primary outcome measure based on routinely recorded data from the blood service information system was the rate of incomplete procedures (< 450 mL collected). Secondary outcomes based on routine data included staff-reported VVR, duration of the collection, failed venous access, venipuncture-related complications, and other complications. Donor return up to 1 year after the index donation will be analyzed separately.

Data preparation and statistical analyses

For study analyses, questionnaire data were linked (by the donation identification number, as attached to the study forms) to routinely collected data. This included donor demographics (gender, age), screening parameters (systolic and diastolic blood pressure, Hb, body weight, and height), and donation data (time and duration of phlebotomy, procedural problems, VVR or other complications, date, fixed vs mobile collection center). Average daily temperature of ≥ 20 °C as recorded at the national weather station (www.knmi.nl) was used to take account of possible effects of very hot days.

Rates of the main outcomes were calculated as overall rates per study group; stratified analyses for first vs 2nd-4th donations (donors making their first donation will be described as new donors and 2nd, 3rd, or 4th donation as novice donors) and male vs female donors were planned. Logistic regression analyses were used to calculate odds ratios (OR) for the study outcomes as binary variables. Initially univariate analysis was performed to examine the effects of gender, age group, very hot days, and mobile vs fixed collection center as categorical variables and EBV and predonation Hb as continuous variables. The final multivariable analysis included those variables which showed statistically significant associations (at the 95% level) in univariate analysis. All analyses were done on an "intention to treat" basis to best approach the real life of blood collection centers; "per protocol" analyses including only donors who drank all the water or squeezed for the whole waiting time were also performed. Statistical analyses were performed using SPSS version 23 (IBM Corporation, Armonk, NY, USA).

Sample size calculation

Based on results in a different study in our organization (unpublished secondary outcome), 15% of VVR were expected to be reported by questionnaire in the target population; a reduction of 25% in reactions could be expected in accordance with the published literature, indicating a need for approximately 830 completed questionnaires in each arm and donation history status.

Protocol modification in the course of the study

Inclusion did not progress as rapidly as anticipated, with eligible donors not being approached due to time constraints of the blood service staff. For this reason, after 6 months it was decided that there should be an intervention switch to revive staff interest and allow us to include donors once for each intervention. The change of intervention occurred in July 2015. At the same time, a control group was introduced of donors in the clusters of a third region of the country who received standard care and gave consent for the questionnaire.

RESULTS

A total of 10,250 donors enrolled. After elimination of forms from donors who did not participate because of deferral or administrative reasons (e.g., illegible email address), 8,879 donors were sent the questionnaire and 2,615 (29%) were sent reminders after initial non-response. Further data cleaning after conclusion of the study resulted in a study group of 8,300 donors (Fig. 1). Demographics and basic donation statistics for study donors are given in Table 1 in comparison to data for all Dutch donors younger than 30 making their 1st to 4th whole blood donation during the study period, showing representativeness of the study groups.

A total of 6,921 questionnaires were returned within 28 days of the index donation, representing a response rate of 83%. The response rate was slightly higher at 86% in the two water groups and 82% in the placebo group in comparison to 78% among questionnaire-only donors.

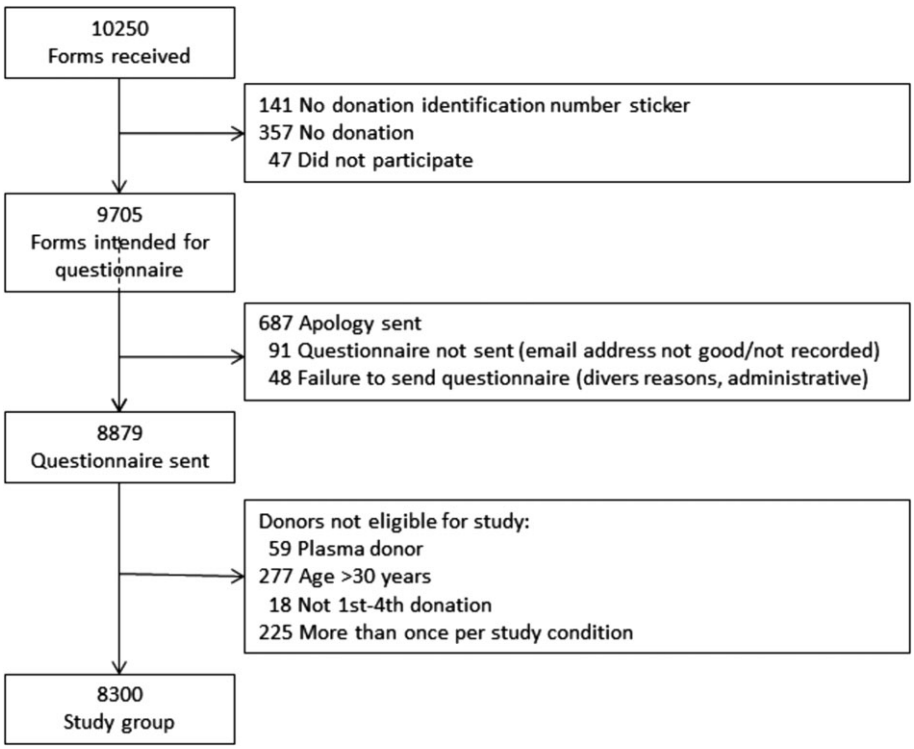

Fig. 1. Flow chart of donors and reasons for non-inclusion.

Compliance and acceptability of interventions

Compliance with the intervention was recorded on 98% of forms; among donors for whom the data was recorded, 92% of donors in the water groups drank all the water (94% in the 330 mL group, 89% in the 500 mL group). In the 500 mL group, 11.1% of responding donors stated that the volume was too large; in the 330 mL group this was 3.4% ($p < 0.001$), while 4.5% said it wasn't enough. All study

TABLE 1. Demographics for study donors and total whole blood donations from donors < 30 years old

Numbers of donations N; % of total	Whole blood donations < 30 years, 1st-4th donations, NL*		Donors in study							
			500 mL		330 mL		Ball squeezing placebo		Questionnaire only control	
Total	77813		2006		2291		1838		2165	
F	54127	69.6%	1403	69.9%	1710	74.6%	1308	71.2%	1611	74.4%
1st donation†	29197	37.5%	843	42.0%	1015	44.3%	634	34.5%	921	42.5%
2nd	20889	26.8%	504	25.1%	612	26.7%	537	29.2%	599	27.7%
3rd	15623	20.1%	361	18.0%	389	17.0%	375	20.4%	372	17.2%
4th	12104	15.6%	298	14.9%	275	12.0%	292	15.9%	273	12.6%
Age (years)‡										
18	7855	10.1%	260	13.0%	275	12.0%	225	12.2%	216	10.0%
19–22	35019	45.0%	949	47.3%	1097	47.9%	894	48.6%	1011	46.7%
23–30	34939	44.9%	797	39.7%	919	40.1%	719	39.1%	938	43.3%
EBV§	M 5.5	(0.57)	M 5.5	(0.55)	M 5.5	(0.58)	M 5.5	(0.52)	M 5.5	(0.56)
Mean (SD) in L	F 4.2	(0.49)	F 4.2	(0.48)	F 4.3	(0.49)	F 4.3	(0.46)	F 4.2	(0.46)
Hb	M 9.5	(0.61)	M 9.5	(0.59)	M 9.5	(0.58)	M 9.5	(0.61)	M 9.5	(0.61)
Mean (SD) in mMol/L	F 8.4	(0.49)	F 8.5	(0.50)	F 8.5	(0.50)	F 8.5	(0.49)	F 8.5	(0.51)
Mobile collection‖	9956	12.8%	247	13.1%	113	5.0%	24	1.4%	146	6.8%
Very hot day	4913	6.3%	54	2.7%	81	3.5%	93	5.1%	94	4.3%

* During study recruitment period.
† According to the study protocol, analyses were performed separately for 1st donations and for 2nd-4th donations.
‡ It was intended that donors should be younger than 30 years of age, however it was found that 112 donors aged 30 had been invited to participate and these donors were not removed during data cleaning.
§ EBV available for 96% of donors.
‖ Mobile collections are not evenly spread over the country and this could have led to uneven distribution over study groups. Sensitivity analyses excluding results from mobile collections showed similar results (data not shown).

group donors were included in the main analyses; the per protocol group consisted of 3,943 donors who drank the whole bottle. Questionnaire responses were received from 3,422 (87%) of this group.

Effect of interventions

Routinely recorded data

In the donation records in the blood service computer system (i.e., including donors who did not respond to the questionnaire), 4.0% of the study donors had incomplete collections (5.4% for first donations and 3.1% for 2nd-4th donations; the rates were 6.4% in the questionnaire group and 3.2% in the intervention groups with non-significant inter-group differences [Table 2A]).

In the routine data, staff-reported VVR occurred in approximately 5% of new donors without significant differences between the groups (Table 2A). There was a trend of reduced staff-reported VVR in novice donors in the two water groups which neared statistical significance with a combined OR of 0.70, 95% CI 0.47–1.05 after adjustment for gender, Hb level and EBV.

Self-reported VVR

The self-reported VVR rates as assessed by the questionnaire in the intervention and questionnaire groups are shown in Table 2B. Overall, 18.5% of responding donors reported VVR symptoms. The rates were similar in the two water groups at approximately 19.5% in new donors, with no significant difference from the placebo and questionnaire groups. VVR were reported by 15.3% and 15.0% novice donors in the 500 mL and 330 mL groups, respectively, giving unadjusted OR for a reaction of 0.75, 95% CI 0.59–0.94 and 0.73, 0.58–0.91, respectively compared to the questionnaire group. Among novice donors who had drunk all the water, the rates were 14.2% and 14.4% respectively in the 500 and 330 mL groups. Since there was no suggestion of a greater effect of 500 mL, we pooled the two water groups in the main regression analyses. In new donors there was no significant effect on VVR in the intervention groups in comparison to controls; in novice donors the OR for the combined water groups in comparison to the control group was 0.74, 95% CI 0.60–0.89, and 0.77, 0.63–0.94, after adjustment for gender, predonation Hb and EBV. The placebo intervention (ball squeezing) did not have a significant effect on VVR.

VVR with loss of consciousness

In all, 135 (1.9%) of the donors who responded to the questionnaire reported that they had fainted; 89 (66%) times the fainting occurred on site. There was no difference in incidence rate between the study groups.

Delayed VVR

Out of all the VVR, 52% were reported as having occurred after the donor left the collection center: 55% of VVR in women and 30% of reactions in men, with no differences between 1st and 2nd-4th donation. There was no significant difference in rates of late VVR between the study groups, either in new or in novice donors (Fig. 2).

Venipuncture-related and other complications

Besides VVR, various complications were reported by the study donors and these are summarized in Table 3. There

TABLE 2A. Rates of unsuccessful collection and vasovagal-type reactions (VVR) per study group (routinely recorded data from computer system)

First donation Total no in group (% female)	Water 500 ml 843 (69.9% F)		Water 330 ml 1015 (76.4% F)		Ball squeezing placebo 634 (72.4% F)		Questionnaire only control 921 (74.7% F)		OR, 95% CI for water in comparison to control		OR, 95% CI for placebo in comparison to control	
Incomplete donation	32	3.8%	55	5.4%	24	3.8%	74	8.0%	**1.78**	**1.29-2.45***	**2.22**	**1.38-3.55***
Female	*21*	*3.6%*	*46*	*5.9%*	*15*	*3.3%*	*58*	*8.4%*				
Male	*11*	*4.3%*	*9*	*3.8%*	*9*	*5.1%*	*16*	*6.9%*				
Staff recorded VVR	44	5.2%	49	4.8%	36	5.7%	57	6.2%	0.80	0.57-1.12	0.91	0.59-1.40
Female	*27*	*4.6%*	*34*	*4.4%*	*26*	*5.7%*	*45*	*6.5%*	0.83	0.59-1.17†	0.96	0.62-1.49†
Male	*17*	*6.6%*	*15*	*6.3%*	*10*	*5.7%*	*12*	*5.2%*				
2nd-4th donation Total no in group (% female)	**1163 (70.2% F)**		**1276 (73.3% F)**		**1204 (70.5 F)**		**1244 (74.2% F)**		**OR, 95% CI for water in comparison to control**		**OR, 95% CI for placebo in comparison to control**	
Incomplete donation	24	2.1%	33	3.6%	30	2.5%	64	5.1%	**2.24**	**1.56-3.22***	**2.08**	**1.34-3.24***
Female	*20*	*2.5%*	*25*	*2.7%*	*24*	*2.8%*	*57*	*6.2%*				
Male	*4*	*1.2%*	*8*	*2.3%*	*6*	*1.7%*	*7*	*2.2%*				
Staff recorded VVR	20	1.7%	39	3.1%	57	4.8%	42	3.5%	0.68	0.46-1.00	1.41	0.94-2.09
Female	*16*	*2.0%*	*26*	*2.8%*	*46*	*5.5%*	*32*	*3.6%*	0.70	0.47-1.05†	1.39	0.93-2.08†
Male	*4*	*1.2%*	*13*	*3.8%*	*11*	*3.1%*	*10*	*3.1%*				

* Odds for complete collection.

† Adjusted for gender, pre-donation hemoglobin, estimated blood volume (EBV); EBV was missing for 205 1st donations and 316 2nd-4th donations.

TABLE 2B. Rates of vasovagal-type reactions (VVR) per study group reported by donors who responded to the questionnaire

1st donation No in group (% female, F)	Water 500 ml 724 (70.7% F)		Water 330 ml 874 (76.7% F)		Ball squeezing placebo 509 (73.4% F)		Questionnaire only control 706 (75.4% F)		OR, 95% CI for VVR, water in comparison to control		OR, 95% CI for VVR, placebo in comparison to control	
Self-reported VVR (Total)	143	19.8%	171	19.6%	116	22.8%	134	19.3%	1.03	0.82-1.28	1.24	0.94-1.64
Female	*111*	*21.7%*	*144*	*21.4%*	*96*	*25.8%*	*111*	*20.9%*	1.06	0.84-1.33*	1.29	0.97-1.72*
Male	*32*	*15.1%*	*26*	*12.7%*	*20*	*14.4%*	*23*	*13.1%*				
Subgroup self-reported Faint	22	3.0%	16	1.8%	9	1.8%	18	2.6%	0.93	0.52-1.63	0.69	0.30-1.54
Female	*18*	*3.5%*	*13*	*1.9%*	*9*	*2.4%*	*16*	*3.0*	0.91	0.51-1.63*	0.80	0.35-1.80*
Male	*4*	*1.9%*	*3*	*1.5%*	*0*	*0%*	*2*	*1.2%*				
Subgroup late VVR	71	9.8%	98	11.2%	57	11.2%	54	7.6%				
Female	*63*	*12.3%*	*93*	*13.7%*	*51*	*13.7%*	*49*	*9.2%*				
Male	*8*	*3.8%*	*6*	*2.9%*	*6*	*4.3%*	*5*	*2.9%*				
2nd-4th donation **No in group (% female, F)**	**Water 500 ml** **1102** **(70.4% F)**		**Water 330 ml** **1107** **(74.0% F)**		**Ball squeezing** **1001** **(71.1% F)**		**Questionnaire only control** **998 (75.3% F)**		**OR, 95% CI for VVR water in comparison to control**		**OR, 95% CI for VVR, squeezing in comparison to control**	
Self-reported VVR (Total)	153	15.3%	165	14.9%	203	20.3%	194	19.4%	**0.74**	**0.60-0.89**	1.05	0.85-1.31
Female	*149*	*19.7%*	*145*	*17.7%*	*175*	*24.6%*	*171*	*22.7%*	**0.77**	**0.63-0.94***	1.12	0.89-1.41*
Male	*14*	*4.7%*	*20*	*6.9%*	*28*	*9.7%*	*23*	*9.3%*				
Subgroup self-reported Faint	19	1.9%	15	1.4%	18	1.8%	18	1.8%	0.89	0.50-1.59	1.0	0.51-1.93
Female	*18*	*2.5%*	*12*	*1.5%*	*16*	*2.2%*	*12*	*1.6%*	0.96	0.54-1.70*	0.99	0.51-1.94*
Male	*1*	*0.3%*	*3*	*1.0%*	*2*	*0.7%*	*6*	*2.4%*				
Subgroup late VVR	94	9.4%	102	9.2%	112	11.2%	93	9.3%				
Female	*87*	*12.3%*	*92*	*11.2%*	*104*	*14.6%*	*88*	*11.7%*				
Male	*7*	*2.4%*	*10*	*3.5%*	*8*	*2.8%*	*5*	*2.0%*				

* Odds ratio adjusted for gender, pre-donation hemoglobin level (mMol/L), estimated blood volume (EBV, in L) as continuous variables; EBV was missing for 170 1st donations and 277 2nd-4th donations.

were differences between female and male donors, for instance, moderate to severe symptoms from hematomas were reported by 12% of female donors and 6% of male donors. For none of these complications were there differences between intervention groups. The rates of self-reported complications were considerably higher than the rates of staff-recorded complications: hematomas were recorded by staff in the computer system for 0.2% of the same group of donors. In all, 16% of donors reported no symptoms at all from their donation (not even at the lowest level): 11% of female and 30% of male donors. Both new and novice female donors in the water groups were less likely to have suffered symptoms than in the questionnaire-only group; symptoms were also less likely for novice female donors in the placebo group than for controls. Male novice donors were less likely to have symptoms in the water groups but there was no effect at a first donation or with squeezing (placebo).

DISCUSSION

This large controlled intervention study showed that in young Dutch WB donors, a water drink of 330 or 500 mL shortly before their 2nd, 3rd, or 4th blood donation reduced self-reported VVR by 23% (95% CI 6–37%) after adjustment for sex, Hb, and EBV. This reduction was only visible in the early reactions (occurring on site) and not in reactions that occurred later. The reduction was not seen among donors donating for the first time. There was no difference between the effects of 330 and of 500 mL, even among those donors who were documented as having drunk all the water. The likelihood of reporting bias from incomplete response to the questionnaire is reduced by the finding of a similar reduction in routinely staff-reported VVR in the whole study group.

Regarding the outcome of successful donation, the rate of incomplete collections tended to be lower in both water groups as well as placebo in comparison to the questionnaire-only group. However, figures are small and we cannot exclude inclusion bias because staff may not have consistently forwarded forms from unsuccessful collections to the administrative center.

In all, the majority of donors reported one or more symptoms which were mostly mild. In the water groups there were more novice donors (both female and male) who reported no symptoms than in the control group. Interestingly, new female donors who had drunk water as well as novice female donors in the placebo group reported slightly fewer symptoms overall. The planned analysis of donors' return behavior may give some indication of the impact of minor symptoms in the donors' experience.

Previous work has shown a similar reduction in the occurrence of VVR of 21% in the meta-analysis by Fisher (95% CI 11–30%)[30] or 26% (95% CI 1–45%) in the recent study by Morand et al.[32] There are differences between the studied groups of donors, with the groups in the

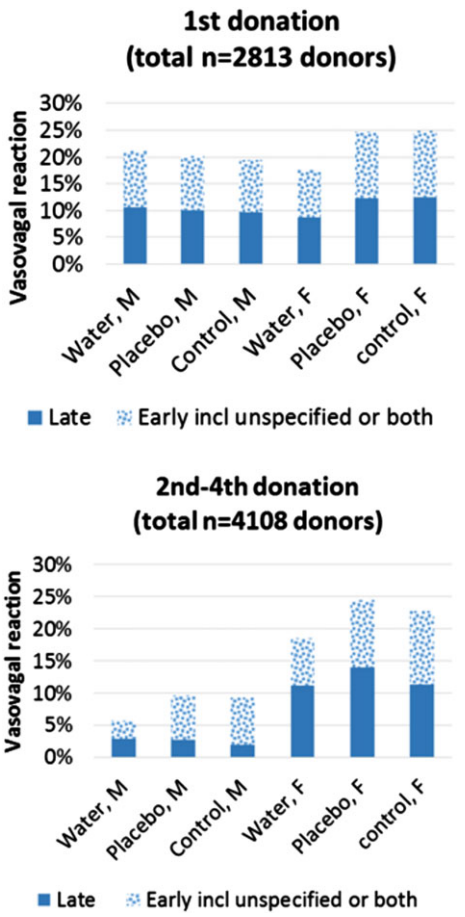

Fig. 2. Incidence of late and early VVR at 1st and 2nd-4th donations. [Color figure can be viewed at wileyonlinelibrary.com]

meta-analysis being mainly younger and inexperienced while the French study included donors of all ages and levels of experience. What is striking in our study is the absence of an effect in new donors. This could be explained by the standard practice in The Netherlands of reclining the donation bed for first donations and having a staff member remain near the bed during the whole donation to provide additional explanations about the donation process and thus distract the donor. In addition, we require the new donor to remain seated on the phlebotomy bed after conclusion of the collection and serve them a drink on the bed. The overall rate of staff-recorded VVR in new donors was 5.4%, comparable to our own results in previous years[1] and slightly lower than those recorded by Eder et al.[37] in donors aged 16–18 after implementation of a minimum EBV of 3.5 L as acceptance criterion in the youngest donors. The absence of an effect of the water intervention is surprising given the positive results in first-time donors found by Newman and others.[31] We hypothesize that the extra care given to new donors in our routine practice is already having as good an effect as could be achieved with extra water before the donation. Alternatively, it is conceivable that effects of the intervention were outweighed by a higher level of fear and stress at the first donation in the Dutch setting.

What is important is the discovery of a reduction of self-reported VVR in novice donors in the water groups, a reduction which was demonstrated in both the 330 mL and 500 mL groups. Although most donors found 500 mL acceptable, the smaller volume was associated with significantly fewer comments of dissatisfaction with the large volume. The smaller volume is potentially cheaper and less onerous for the majority; donors wishing to drink more could refill their bottle or glass.

Our avoidance of a focus on VVR prevention in the study performance and the inclusion of a comparison group of donors who received a control intervention constitute important strengths of this study. The actual mechanism by which a water drink reduces the occurrence of VVR has been postulated but not proven to be mediated by a sympathetic reflex; a psychological effect from the extra attention however remains an additional possibility.[20,31,39,40]

As described in the results, there was no reduction in the occurrence of VVR after the donor had left the collection center. In fact, over half the VVR were reported to have started off-site. These late reactions are concerning because they occur at a time when staff cannot provide treatment and they can lead to accidents. Overall, the late VVR appear to have been milder, with the affected donors reporting a lesser degree of dizziness or nausea and the proportion of donors who said they had fainted also being less than with on-site VVR (data not shown). However, this was not a prespecified analysis. One would not expect a water drink to have a noticeable affect hours after the donation. Wieling et al.[28] suggest that pre-donation salt loading or isotonic fluid may be more effective in preventing VVR or might have a longer effect than plain water on the basis of physiological mechanisms. Morand et al.[32] found a reduction of delayed VVR and of post-donation fatigue in the donors who were given isotonic fluid. However, the higher costs of proprietary sports drinks and likely lower acceptance of isotonic fluid by donors, make a simple water drink a more likely intervention for broad adoption. Some blood establishments additionally offer a salty snack, and this potentially combines the benefits of water drinking with those of salt loading.[28,29]

A limitation of our study must be noted: because no extra support for staff members was provided at collection-center level, recruitment was sluggish and sometimes incomplete which could have introduced bias if staff avoided including donors on busy days. However, if this happened equally in the intervention and control groups, this should not invalidate the comparisons. Despite the possibility of recruitment bias, our data show that study groups are broadly comparable to the whole group of potentially eligible donors and that demographics were similar in all the arms. The percentage of participants donating in mobile centers was slightly lower than nationwide which could be a

TABLE 3. Other self-reported donation complications

	Water		Ball squeezing placebo		Questionnaire only control	
Total no in group	3707		1510		1708	
Females, 1st donation	1182		371		531	
Tiredness	336	28.5%	109	29.4%	148	27.9%
Headache	91	7.7%	32	8.6%	37	7.0%
Hematoma	136	11.5%	48	12.9%	55	10.4%
Delayed bleeding	71	6.0%	25	6.7%	19	3.6%
Tingling	66	5.6%	17	4.6%	22	4.1%
Painful arm	135	11.4%	41	11.1%	62	11.7%
No symptoms	**140**	**11.9%***	38	10.2%	41	7.7%
Males, 1st donation	416		138		175	
Tiredness	64	15.4%	19	13.8%	15	8.7%
Headache	8	1.9%	4	2.9%	6	3.5%
Hematoma	11	2.6%	13	9.4%	9	5.1%
Delayed bleeding	8	1.9%	3	2.2%	3	1.7%
Tingling	11	2.6%	4	2.9%	9	5.1%
Painful arm	21	5.0%	6	4.3%	12	6.9%
No symptoms	118	28.4%	35	25.4%	46	26.3%
Females, 2nd-4th donation	1526		712		752	
Tiredness	357	23.4%	195	27.4%	229	30.4%
Headache	109	7.1%	52	6.0%	44	5.8%
Haematoma	161	10.6%	73	10.6%	95	12.7%
Delayed bleeding	105	6.9%	53	7.4%	46	6.1%
Tingling	66	4.3%	25	3.5%	22	2.9%
Painful arm	198	13.0%	92	13.0%	83	11.1%
No symptoms	**203**	**13.3%***	**90**	**12.6%***	63	8.4%
Males, 2nd-4th donation	583		289		246	
Tiredness	65	11.1%	30	10.4%	26	10.5%
Headache	8	1.4%	7	1.6%	4	1.6%
Haematoma	23	3.9%	11	3.8%	13	5.3%
Delayed bleeding	18	3.1%	16	5.6%	8	3.2%
Tingling	12	2.1%	14	4.9%	2	0.8%
Painful arm	32	5.5%	23	8.0%	17	6.9%
No symptoms	**211**	**36.2%***	81	28.0%	64	26.0%

* $p < 0.05$ in comparison to questionnaire only.

consequence of higher workload as well as regional variation in proportion of mobile collections. The outcome of self-reported VVR was robust to adjustment for donation in a mobile center in multivariable analyses, as well as to exclusion of mobile attendances from the analyses. However, under-representation of mobile donations reduces certainty that our findings are applicable to that setting. A further limitation lies in the relatively large number of donors who for administrative reasons had to be excluded because they were not sent the questionnaire in a timely fashion. This was, however, totally unrelated to donor demographics so would not invalidate the findings. Despite the limitations, important strengths are the large size of the study, its year-round inclusion, and the excellent response to the questionnaire.

The present findings provide evidence to support a recommendation that younger, inexperienced donors drink approximately 330 mL of water before their WB donation. Moreover, the demonstrated feasibility and the near-zero costs of the measure in routine blood collection settings make it attractive for pragmatic use in other groups of donors. Notwithstanding the need for further work regarding possible other beneficial measures, the findings of this study provide evidence to the worldwide blood collection community of the benefit of ensuring that water is prominently available in collection centers, that all staff encourage donors to drink shortly before their donation, and that the donor information materials reinforce the message.

CONCLUSION

In this large intervention study embedded in routine blood collection practice, over 90% compliance was achieved with drinking 330 or 500 mL of water in the wait immediately before phlebotomy. Water drinking had no effect on VVR in first donations but was associated with a 23% reduction of self-reported VVR in WB donors aged up to 30, making their 2nd, 3rd, or 4th donation. There were no differences in VVR between the two volumes of water.

APPENDIX A

Appendix: Questionnaire

A few days ago you donated blood. Thank you very much for your donation!

We are conducting a research project at your collection center. For this we make use of the routinely recorded

information about the donation e.g.*, whether the collection was successful and how long it took. We would be grateful if you would help by replying to the questions below. Filling in the questionnaire will only take a few minutes of your time. There are no right or wrong answers. Your answers will only be used for the study and will not be passed on to the blood bank staff.*

(Water group)

Before your last donation we asked you to drink a bottle of water. How did you find drinking the bottle of water?

(Free text)

What did you think of the quantity of water which we gave you?

1. Too much
2. Enough
3. Not enough
4. None of these alternatives, (free text comment)

Did you drink anything in between the health screening interview and the start of your donation?

1. Yes, I drank all of the bottle of water which I was given.
2. Yes, I drank part of the bottle of water which I was given.
3. Yes, I drank all of the bottle of water which I was given and I drank some more as well.
4. No.
5. I can't remember.

(Ball squeezing placebo group)

Did you exercise your arm by squeezing a ball?

1. Yes, the whole time until I was called for my donation.
2. Yes, part of the time until I was called for my donation.
3. No.
4. I can't remember.

(Ball squeezing placebo group *and* questionnaire-only control group)

Did you drink anything in between the health screening interview and the start of your donation?

- Yes
- No
- I can't remember

(If yes) Please describe what type of drink you took and how much you drank.

(All donors)

Usually blood donations do not give donors any problems. Sometimes a donor may have symptoms from their donation. This can happen during the donation, immediately afterwards or later, after you have left the collection center. The next questions are about possible symptoms.

During or after your recent blood donation, were you troubled by one or more of the following?

Bleeding at the needle entry site?

1. not at all.
2. slightly.
3. moderately.
4. severely.
5. to an extreme degree.

A bruise on your donation arm? (1-5).
A painful arm? (1-5).
Tingling or a radiating sensation in your forearm? (1-5).
Tiredness? (1-5).
For how long were you more tired than usual (in hours or days)?
During or after your donation, were you troubled by dizziness or lightheadedness? (1-5).

When did you feel the dizziness?

1. At the collection center
2. While returning from my donation
3. At home
4. At work
5. Somewhere else

Did you suffer from a headache during or after your donation?
When did you have the headache? (At the collection center, while returning .....)
During or after your donation, were you troubled by nausea? (1-5).
When did you feel the nausea? (At the collection center, while returning .....)
Did you faint during or after your donation?
When did you faint? (At the collection center, while returning .....)

Please contact the blood bank to tell them about this if necessary.

Did the donor assistant recline the bed for you? (Yes, no, don't know).
Did you have to sit, lie down, or rest? (Yes, no, don't know).
Did you have other physical symptoms or problems during or after your donation?

Please contact the blood bank to tell them about this if necessary.

Do you have any other remarks or questions? Please tell us about them here (free text).

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