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Original Article

Transfusion Medicine Section

Role of Predonation Hydration in the Prevention of Postdonation Vasovagal Reactions in First Time Blood Donors: A Randomised Controlled Trial

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ABSTRACT

Introduction: A crucial component of the effort to meet the growing demand for blood is the recruitment and retention of young novice blood donors. Reducing postdonation syncopal reactions could have a beneficial impact on donor convenience, safety, and desire to donate again.

Aim: To evaluate the effectiveness of predonation hydration over standard blood donation in the prevention or decrease in severity of postdonation Vasovagal Reactions (VVR) in hydrated blood donors in comparison with the non hydrated group.

Materials and Methods: The randomised controlled trial was conducted on 953 first time voluntary blood donors. Donors in the intervention arm drank 250 mL water 30 minutes before blood donation, while those in the control group did not receive any intervention. Blood was collected by standard protocol. Outcome, VVR, if present was graded as mild, moderate, and severe. Analysis of results were done using Statistical Package for the Social Sciences (SPSS) version 16.0. A sensitivity analysis was also done to consider the dropouts from the study.

Results: A total of 900 participants were included in the study, of which 443 were controls and 457 were cases. An effect size of 6.1%, a Relative Risk (RR) of 0.54 {95% Confidence Interval (CI)=0.36-0.81} and a risk reduction of 45% was arrived at, pointing to a protective role for predonation hydration in preventing VVR. There was a significant reduction in the severity of VVR in the predonation hydration group compared to the standard blood donation group (p-value=0.002). The protective effect of hydration on decreasing the occurrence and severity of VVR had statistical support in males in the moderate and severe grades (p-value=0.017). A similar statistical significance was not established in females (p-value=0.173). Sensitivity analysis did not reveal a difference in the statistical significance of variables between compared groups.

Conclusion: Predonation hydration was found to be effective in preventing and decreasing the severity of VVR in novice blood donors.

Keywords: Loss of consciousness, Syncope, Vasovagal reaction

INTRODUCTION

In this era of spreading transfusion transmissible diseases the safest and most reliable donor is the repeat voluntary donor. This forms a small pool of committed volunteers. Thus, there is a clear need to enhance recruitment and retention of young novice blood donors to strengthen the donor pool.

There are a number of factors that shape individual decision to re-donate. The experience of syncopal reactions (which can vary in severity from mild dizziness, sweating and light headedness to complete Loss of Consciousness (LOC) is a particularly important barrier to blood donor retention [1-3]. Considering all donors of different ethnic groups as one single unit, in 2004, total donor reactions came to 12.1%, in 2005 it came to 10.9%, and 11.5% for the combined 2004 and 2005 statistics [1-4]. The Blood Donor Return Rates (BDRR) from donations inducing a VVR and fatigue were significantly lower than BDRR from donations with no VVR {Probability (P)=0.002}. Reducing such syncopal reactions could have a beneficial impact on donor convenience, safety, and desire to donate again, contributing to a safe donor pool. In this scenario, interventions which are targeted against decreasing the occurrence of adverse donor reactions, assume additional importance [4-6].

More than predonation care to prevent syncopal reactions, current strategy at blood centres is to provide refreshments after blood donation. A number of interventions like intake of caffeine, applied muscle tension to leg muscles, distraction of the donor, have been tried with variable benefits. Interventions as applied muscle tension to calf muscles during blood donation have shown to reduce the incidence of VVR [8]. However, predonation salt loading did not give a statistically significant decrease in VVR [9]. Studies on predonation hydration to reduce the incidence of postdonation VVR have to be given special emphasis, considering the nature of the intervention which is cheap, easily administered, without complication of its own, and applicable in a day-to-day setting [7-9]. The present study aimed to evaluate the effectiveness of predonation hydration over standard blood donation to prevent or decrease the severity of postdonation VVR in hydrated blood donors in comparison with the non hydrated group.

MATERIALS AND METHODS

This randomised controlled trial with outcome assessor blinding was conducted for three months from May 2014 to July 2014, at the Transfusion Medicine Department of a tertiary care cancer hospital at Kerala, India. Approval for the study was obtained from the Institutional Review Board (IRB/03-2014/03-18th March, 2014) and Human Ethics Committee of the institute of affiliation (HEC No.17/2014 dated 9/5/2014).

Sample size calculation: A preliminary assessment of the number of first time blood donors who experienced any form of VVR was done over one month at the institute. The prevalence was 9.5%. The effect difference was estimated to be 50%, that is, reduction in vasovagal syncope from 9.5% to 4.75%, to be operationally significant. Using an event rate of p (p1) to be 9.5% in the control arm and 4.75% (p2) in the intervention arm, for a two-sided p-value ≤0.05

and power 80%, a sample size of 453.67 (rounded to 455) first time donors in each arm was calculated using the formula:

$$N=\frac{p_1(100-p_1)+p_2(100-p_2)}{(p_2-p_1)^2}\times(Z_\alpha+Z_\beta)^2$$

Where, p_1: stands for percentage of syncope in the standard treatment, p_2: stands for percentage of syncope in the experimental treatment, (p_2-p_1) is the clinically meaningful effect size, N: stands for sample size.

A total of 963 first time donors, both males and females, in the age group 18 to 55 years, who met all donor eligibility criteria given in the donor questionnaire, and subsequent physical examination, were assessed for enrolling into the study after obtaining informed written consent. (Guidelines on assessing Donor suitability for blood donation (World Health Organisation {WHO} 2012) [10].

Inclusion criteria: Those first time voluntary donors who met all donor eligibility criteria from questionnaire and during physical examination between age group of 18 to 55 years both male and female were included in the study.

The participants of this study consisted of predominantly young college students donating for the first time. Novice donors were chosen because they are an ideal population for testing potential reaction-reducing interventions, since first time donors experience significantly more reactions [11-13].

Exclusion criteria: Donors with history of VVR due to any reason other than blood donation and donors without informed consent and not willing to participate were excluded from the study. Total 53 donors were excluded from study (three had experienced febrile fits during childhood, two gave history of antiepileptic medication, the rest 48 failed to consent for the study when they were explained the procedure).

Study Procedure

The sampling method adopted was simple randomisation using random number table. Random number sequence generation and preparation of sealed paper slips was done by research assistant, who was kept unaware of the allocation with respect to random numbers.

Donors, who satisfied all criteria for blood donation, were asked to choose one sealed paper slip from the lot. On opening the sealed slip, the donor was allocated to control group if the number on it was odd, and to intervention group if the number was even. After randomisation, a donor was allowed to discontinue from the study if continuing in the study was not in his or her best interest [Table/Fig-1]. Seven donors from the control group and three donors from the intervention group had to be excluded, hence a total of 900 donors who conformed to all criteria were obtained.

Gender	Intervention	Control
Male	Time constraints-1	Demise of relative-1
	Could not drink water fully-1	Time constraints-2
		Undercollection-2
Female	Anxiety on being part of study-1	Fainted on seeing needle-1
		Undercollection-1

[Table/Fig-1]: Cases excluded from study.

Intervention decided upon was 250 mL of bottled water which the donor would consume fully as quickly as he could. Donors in the control group did not receive any intervention [14-16]. Donors of both groups were asked to wait for 30 minutes before they were called into the blood collection room for blood donation. This was to allow for significant cardiovascular changes, including increases in vascular constriction and blood pressure that peak approximately 30 minutes after consuming fluids, and persists for about one hour.

Blood was collected by the standard protocol. A 350 mL of whole blood was drawn into blood bags containing 49 mL of Citrate Phosphate Dextrose Adenine (CPDA) anticoagulant. The staff nurse at the blood collection room who was the outcome assessor was blinded as to which donor belonged to what group. Primary outcome was a dichotomous variable of yes or no for VVR. The secondary outcome was the severity of VVR which was recorded as an ordinal variable of mild, moderate, and severe, according to the criteria by American Association Blood Banks (AABB) working classification [17,18].

Classification of Vasovagal Reactions (AABB) [17,18]

1. Mild vasovagal reactions (No LOC): Cold extremities, chills, feeling of warmth, hypotension, extreme light-headedness, dizziness, nausea, vomiting, pallor (pale skin and lips), slow or rapid pulse, twitching.

2. Moderate vasovagal reactions (LOC uncomplicated): Symptoms and signs of mild category plus LOC for less than 60 seconds.

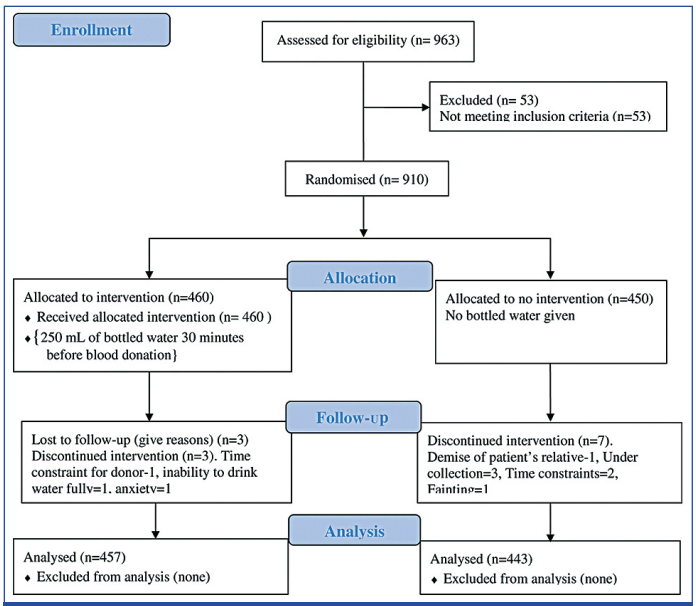
3. Severe vasovagal reactions: Symptoms and signs of moderate category plus LOC more than 60 sec, loss of bowel/bladder control, tetany.

4. Severe vasovagal reactions with injury: Symptoms and signs of severe vasovagal reactions plus an injury or fall.

Outcome assessment and grading was done and recorded in the donor reaction injury report form by the phlebotomy nurse, who was blinded to the group to which a donor belonged. The events were graded as O, grade 1 (Mild), grade II (Moderate), grade III (Severe), and sufficient remedial measures were given.

STATISTICAL ANALYSIS

There were 10 dropouts from the study, whose postdonation data could not be collected[19] (3 in the intervention group and 7 in the control group). Hence, method of analysis followed was Per Protocol [Table/Fig-2].



[Table/Fig-2]: CONSORT flow chart.

Data was analysed and statistical analysis was done using SPSS version 16.0. The main analytical test applied was Chi-square. Primarily, the adequacy of randomisation of the participants with respect to baseline variables was looked for. The first step in data analysis was to assess the descriptive statistics of the baseline variables of the participants in the two arms of the treatment and to ensure that randomisation was proper. For quantitative variables as body weight and Body Mass Index (BMI) with normal distribution, mean and standard deviations were calculated. Independent t-test was used to test for adequacy of randomisation. Age showed a skewed distribution; hence median and inter-quartile range were calculated. Mann-Whitney U test was used to test for adequacy of randomisation. For qualitative

variables, percentage was calculated. Chi-square analysis test was used to compare the baseline categorical variables.

RESULTS

A total of 900 subjects participated in the present study, of which 443 were control group and 457 were intervention group with a mean age of 26.56 (6.9) years and 27.10 (7.5) years, respectively. It was seen that the groups were comparable with respect to all demographic variables age, gender, body weight, and BMI {[Table/Fig-3]: Adequacy of randomisation}.

Variables		Control (n=443)	Intervention (n=457)	Test value	p-value
Mean age (years)		26.56 (6.9)	27.10 (7.5)	-	0.478 (Mann-whitney U)
		444.27	456.54		
Age category (years)					
Group 1	≤19	58	58	3.515	0.172 (Chi-square)
Group 2	20 to 29	262	258		
Group 3	30 to 39	100	103		
Group 4	≥40	23	38		
Gender					
Female		33	24	11.831	0.112 (Chi-square)
Male		410	433		
Weight (Kg) Mean (SD)		70.26 (11.5)	70.72 (11.9)	-0.586	0.558 (Independent t-test)
BMI (kg/m^2)					
Mean±SD		26.365±2.8	26.37±3.04	-0.054	0.957 (Independent t-test)
SE		0.137	0.142		
Median		26.2	26.14		
BMI grade					
0		147	157	1.207	0.751 (Chi-square)
2		247	247		
3		49	53		

[Table/Fig-3]: Adequacy of randomisation.
SD: Standard deviation; Kg: Kilogram; m: Meter; SE: Standard error; BMI: Body mass index

Association between hydration and outcome [Table/Fig-4]

Odds ratio (OR) and CI {0.507 (0.324-0.793)} also showed a protective effect for predonation hydration to prevent VVR (p=0.003). The number of hydrated individuals who need to donate to predict occurrence of one VVR was 16.4.

Association between hydration and severity of outcome [Table/Fig-5]

The few outcomes that occurred after intervention were more of the mild category. Risk of outcomes was lower in the higher outcome grades, with risk of zero for grade 3 or severe outcome. There were six severe outcomes in the non hydrated group, but no severe outcome in hydrated group. There was a significant decrease in the occurrence and severity of VVR in the hydrated group in comparison with the non hydrated group (p=0.002). In the mild reaction category, RR and 95% CI do not reveal a significant protective effect for hydration. In the moderate reaction category, the protective effect for predonation hydration is reflected in both OR=0.2869 and RR=0.29.

The association between hydration and outcome in males is supported by RR and OR also with a protective effect (p=0.013), OR=0.555 (0.34-0.888). Protective effect is not evident in females (p=0.074), OR=0.242 (0.047-1.247) [Table/Fig-6]. In male gender, mild and moderate reactions are seen in hydrated donors, but severe reactions are absent [Table/Fig-7]. Hydrated females experienced only mild reaction. A statistically significant relationship between hydration and severity of reaction could be established only in males (p=0.017) and not in females (p=0.173).

Hydration	Vasovagal reactions				Total	Chi-square	p-value
	Nil	Mild	Moderate	Severe			
Yes	424 (92.8%)	27 (5.9%)	6 (1.3%)	0 (0%)	457 (100%)	15.32	0.002
No	384 (86.7%)	34 (7.7%)	19 (4.3%)	6 (1.4%)	443 (100%)		
Total	808 (89.8%)	61 (6.8%)	25 (2.8%)	6 (0.7%)	900 (100%)		
Odds ratio (95% CI)	-	0.72 (0.42-1.2)	0.2869 (0.11-0.72)	0	-		
RR (95% CI)	-	0.73 (0.45-1.19)	0.29 (0.11-0.73)	0	-		

[Table/Fig-5]: Association between hydration and severity of outcome.
CI: Confidence interval

Gender	Hydration	Outcome present	Outcome absent	Chi-square	p-value	OR (95% CI)	RR (95%CI)
Male	Yes	31	402	6.14	0.013	0.555 (0.34-0.888)	0.58 (0.38-0.90)
	No	50	360				
	Total	81	762				
Female	Yes	2	22	3.2	0.074	0.242 (0.047-1.247)	0.30 (0.07-1.2)
	No	9	24				
	Total	11	46				

[Table/Fig-6]: Gender wise association between hydration and outcome.
OR: Odds ratio; RR: Relative risk; CI: Confidence interval

Gender	Hydration	Severity of vasovagal reaction				Total 900	Chi-square
		Nil 808	Mild 61	Moderate 25	Severe 6		
Male	Yes	402 (92.8%)	25 (5.8%)	6 (1.4%)	0	433	10.195 p=0.017
	No	360 (87.8%)	31 (7.6%)	15 (3.7%)	4 (1%)	410	
	Total	762 (89.6%)	56 (6.6)	21 (2.5)	4 (1.3)	843	
Odds ratio			0.72 (0.42-1.24)	0.35 (0.13-0.93)	0	-	
Relative risk			0.73 (0.44-1.27)	0.36 (0.14-0.93)	0	-	
Female	Yes	22 (91.7%)	2 (8.3%)	0	0	24	4.99 p=0.173
	No	24 (72.7%)	3 (9.1%)	4 (12.1%)	2 (6.1%)	33	
	Total	46 (76.7%)	5 (8.3%)	4 (6.7%)	2 (8.3%)	57	
Odds ratio			0.72 (0.11-4.7)	0	0	-	
Relative risk			0.75 (0.13-4.11)	-	-	-	

[Table/Fig-7]: Hydration and severity of outcome (gender).

A protective role of water was reflected only in the age strata 2 (i.e. 20 to 29 years) age group (0.002, OR=0.403 (0.222-0.733) [Table/Fig-8]. Grading BMI into three categories, significant p-value of 0.01

Hydration	Vasovagal reactions		Total	Chi-square	p-value	Absolute risk reduction	Odds ratio (OR)	Relative risk (RR)	NNT (Prevent VVR)
	Yes	No							
Yes	33 (7.2%)	424 (92.8%)	457 (50.7%)	9.112	0.003	13.3%-7.2%=6.1%	0.507 (0.324-0.793)	0.54 (0.36-0.81)	16.4
No	59 (13.3%)	384 (86.7%)	443 (49.3%)						
Total	92 (10.2%)	808 (89.8%)	900 (100)						

[Table/Fig-4]: Association between hydration and outcome.
NNT: Number needed to treat; VVR: Vasovagal reaction

and RR (0.24-0.90) less than one (0.43) was obtained only in the BMI range 18.5 to 25 kg/m^2 category (normal BMI) [Table/Fig-9]. Hydration of donors did not offer protection in the other two BMI categories.

Group	Hydration	Outcome		Sample size	Chi-square	p-value	Odds ratio (95% CI)	Relative risk (95% CI)
		Yes	No					
1 (≤19 years)	Yes	5	53	58	2.610	0.106	0.403 (0.131-1.245)	0.45 (0.16-1.2)
	No	11	47	58				
2 (20 to 29 years)	Yes	17	241	258	9.311	0.002	0.403 (0.222-0.733)	0.44 (0.25-0.76)
	No	39	223	262				
3 (30 to 39 years)	Yes	8	95	103	0.004	0.951	0.968 (0.349-2.688)	0.97 (0.37-2.48)
	No	8	92	100				
4 (≥40 years)	Yes	3	35	38	0.294	0.588	1.886 (0.184-19.287)	1.81 (0.2-16.4)
	No	1	22	23				

[Table/Fig-8]: Association of hydration and outcome based on age strata.

Grade	Hydration	Outcome		Sample size	Chi-square	p-value	Odds ratio (OR) (95% CI)	Relative risk (RR) (95% CI)
		Yes	No					
Grade 1 (18.5 to 25 kg/m^2)	Yes	12	145	157	5.48	0.019	0.424 (0.204-0.883)	O.43 (0.24-0.90)
	No	24	123	147				
Grade 2 (25 to 30 kg/m^2)	Yes	18	229	247	2.39	0.122	0.615 (0.331-1.14)	0.64 (0.36-1.13)
	No	28	219	247				
Grade 3 (30 to 35 kg/m^2)	Yes	3	50	53	2.14	0.14	0.360 (0.088-1.479)	0.39 (0.10-1.4)
	No	7	42	49				

[Table/Fig-9]: Association of Hydration and outcome based on BMI strata.

There was a doubt that Per Protocol analysis excluding the dropouts would affect the robustness of the study, hence to consider the 10 withdrawals from the study, Intention to Treat (ITT) analysis [Table/Fig-10] was also performed [23]. The participants who left the study were considered to continue in the treatment arm they were originally allocated to, to maintain the quality of balancing variables. Two separate analyses were done, considering these dropouts to have had the 'best' or the most favourable outcome (No VVR) and the 'worst' or the most unfavourable outcome (Severe VVR). We looked for any difference in significance of the major parameters analysed, on analysing the dropouts too, in comparison with Per Protocol analysis. By all three analytical methods, OR and RR favour a protective influence for hydration against VVR (p-value (ITT) 0.001, p-value (Per Protocol) 0.002, p-value (Best Case) 0.003}.

Statistical analysis	ITT (Worst case) analysis	Per protocol analysis	Best case analysis
Chi-square	10.695	9.112	8.82
p-value	0.001	0.003	0.003
Effect difference	6.9%	6.1%	5.9%
Risk reduction	0.46	0.45	0.46
NNT	14.4	16.3	16.84
RR (95% CI)	0.61 (0.41-0. 91)	0.54 (0.36-81)	0.4 (0.36-0.82)
OR (95% CI)	0.49 (0.32-0.75)	0.50 (0.32-0.7)	0.51 (0.32-0.80)

[Table/Fig-10]: Sensitivity analysis.
ITT: Intention to treat; NNT: Numbers needed to treat; RR: Relative risk; OR: Odds ratio; CI: Confidence interval

DISCUSSION

The present study examined the effectiveness of water loading in attenuating physiological reactions to blood donation in novice donors. It was hypothesised that participants given a water loading intervention (250 mL of bottled water prior to donation) would have a significant reduction in the incidence of VVR compared to those participants who did not receive this intervention. The participants of this study consisted of predominantly young college students donating for the first time. Novice donors were chosen because they are an ideal population for testing potential reaction reducing interventions, since first time donors experience significantly more reactions [9-12]. As this was a study of the effectiveness of an intervention, the design of the study was chosen to be a randomised controlled trial, which is the most powerful tool available for the evaluation of an intervention.

Hydration before blood donation was found to have a protective role in preventing VVR. This is in agreement with the studies by Wiersum-Osselton J et al., Lu CC et al., New man B et al., Van den Berg K et al., [12,13,14,16]. Although an effect size of 50% was aimed at, only 45% could be achieved. This absolute risk reduction of 6.1% and RR reduction of 45% is in agreement with other similar studies [9,15]. Absolute risk reduction achieved by Newmann B, Van den Berg K et al., across studies ranged from 1% to 6.5% [14, 16]. France CR et al., reported a 9.8% reduction (p-value=0.01) [2].

Secondary objective looked for was the severity of outcome after water loading. There was a significant reduction in outcome rate in the intervention group with p=0.002. No severe reaction or grade 3 was reported in the intervention group whereas six severe outcomes were present in the control group. This points to the definite protective role for water. Thus, the null hypothesis that there is no significant reduction in the severity of VVR in the predonation hydration group compared to standard blood donation group stands rejected.

A definite protection for hydration to prevent VVR could be established only in moderate and severe reaction categories and not in the mild reaction. This could be explained as follows. In the mild reaction category, 95% CI of RR is not seen statistically significant for protection. When the intervention was given, due to the protective effect of the intervention, some of the subjects (donors) in interventional group would have migrated into the mild category who otherwise would have been in the moderate and severe categories (if intervention was not present), along with an actual decrease in the subjects (donors) having a mild reaction. Thus, even though mild outcomes were lessened by intervention, migration from higher grades into mild category could be the reason why 95% CI of RR of mild reaction category does not appear statistically significant as protective.

In the case of male gender, RR and OR for predonation hydration also shows a protective effect. This protective role was not observed in females. This could be due to a small sample size. There was a significant difference in outcome between intervention group and standard group in the age strata 20 to 29 years. This is in agreement with data by Trouern Trend [20,21] that next to body weight, age is the most important factor for VVR. A significant correlation between hydration and VVR was obtained only in the normal BMI category. The findings are in agreement with Yamada T and Yanagimoto S in that, controlling for age, gender, race/ethnicity, and donation status, low BMI was a significant predictor of VVR [22].

Sensitivity Analysis

It was found that there was no difference in the statistical significance between categories, on analysis by ITT, worst case and the best-case analysis.

Strength(s)

The robust design and analysis, relevance of the intervention in day-to-day blood collection from donors in preventing VVR.

Limitation(s)

Limitations of study; Uneven sample distribution across groups: This could be solved by stratified random sampling. Lack of Dose response effect: Even though severity of reactions was much lower in intervention group, the different reaction grades could not be quantified. A dose response effect was not looked into, that is to what

extent the administration of different quantities of water to subjects would have an effect in preventing or decreasing the severity of a VVR. The present study did not look into the effect produced after administration of equal volumes of various fluid types with different rates of gastric emptying and absorption [23]. Lack of placebo for the control group: A true control condition would imply that both the experimental and the control group have the same experience. In the present study the control group did not experience the drinking manipulation at all. The possibility that donors themselves could have consumed water before they came for blood donation could not be established.

CONCLUSION(S)

Predonation hydration is a simple, safe, effective, cheap strategy that can be easily and safely followed by every blood collection service to prevent and decrease VVR. Study, if done on larger and diverse population to determine the beneficial effect of administering varying types of fluids of varying quantity at critical time periods of blood donation will give better generalisability and acceptability to the intervention. The value of decreased VVR would be improved donor safety, better donor retention, higher donor satisfaction and potentially reduced cost.

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