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Full length article

Fluid resuscitation during persistent postpartum haemorrhage and maternal outcome: A nationwide cohort study

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ABSTRACT

Objective: To determine the association between increasing volumes of crystalloids and colloids administered before transfusion of packed red blood cells in women with persistent postpartum haemorrhage and adverse maternal outcomes.
Study design: Retrospective cohort study in the Netherlands. Women with persistent postpartum haemorrhage and known clear fluids volume for resuscitation were included. Women who received ≤2 L of clear fluids were the reference group. We determined the effect of every additional litre of clear fluids on total blood loss, severe maternal morbidity and mortality. Results were adjusted for patient and bleeding characteristics.
Results: Of the 883 included women, 199 received ≤2 L of clear fluids. Median blood loss for the reference group was 2.9 L (interquartile range 2.2–3.4). Adjusted mean difference in blood loss compared with the reference group was 0.2 L (95% confidence interval −0.1 to 0.5) for women in the >2 to ≤3 L, 0.4 L (0.1–0.7) for the >3 to ≤4 L category, 0.6 L (0.5–0.7) for the >4 to ≤5 L category, and 1.9 L (1.5–2.3) for the >5 to ≤7 L category. Adjusted odds ratios for adverse maternal outcomes were 1.0 (0.7–1.6), 1.2 (0.8–1.9), 1.8 (1.1–3.1) and 4.4 (2.6–7.5) for women in the 2 to ≤3 L category, >3 to ≤4 L, >4 to ≤5 L, and >5 to ≤7 L volume categories respectively. Results were similar in strata of different severities of bleeding.
Conclusion: Clear fluids volume >4 L was independently associated with adverse maternal outcome in women with persistent postpartum haemorrhage.

Introduction

Almost 20% of maternal deaths worldwide are due to postpartum haemorrhage, the leading cause of maternal death and morbidity [1,2]. Following childbirth, women are at risk of postpartum haemorrhage, and when postpartum haemorrhage is refractory to first-line therapy, it may deteriorate to severe haemorrhage [3]. Management of postpartum haemorrhage consists of obstetric and haemostatic interventions to stop bleeding, and fluid resuscitation to prevent and treat haemorrhagic shock [3].

During fluid resuscitation, infusion of crystalloids and colloids precedes transfusion of red blood cells. Red-cell transfusion

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during ongoing haemorrhage not only maintains circulating blood volume and tissue oxygenation, but may also support haemostasis by improving coagulation [4–10]. Obviously, red-cell transfusions are also associated with adverse effects including transfusion reactions and transfusion-related acute lung injury [11,12]. And, fluid resuscitation with crystalloids and colloids may worsen maternal outcomes by causing dilution of clotting factors and platelets [13–15]. Moreover, colloid fluids have been associated with dysfunction of clotting factors [16–20]. The effects of fluid resuscitation on patient outcomes have been studied in patients with major trauma or surgery, but not in women with postpartum haemorrhage [18,21–25].

Because of the potential adverse effects of both red-cell transfusion and fluid resuscitation with crystalloids and colloids, timing of switch from fluid resuscitation to resuscitation with packed red blood cells in women with severe postpartum haemorrhage should be carefully balanced. Nonetheless, it is unknown which volumes of crystalloids and colloids potentially worsen maternal outcomes, and therefore, justify switching to red-cell transfusion.

We set out to describe the association between increasing volumes of clear fluids administered before transfusion of packed red blood cells in women with severe postpartum haemorrhage and adverse maternal outcomes.

Materials and methods

Patients

We used the TeMpOH-1 (*Transfusion strategies in women during Major Obstetric Haemorrhage*) study, a nationwide, retrospective cohort study on transfusion strategies in women with major obstetric haemorrhage in the Netherlands. The cohort comprised consecutive women from 61 hospitals who, from 1 January 2011 to 1 January 2013, received either ≥4 units of red blood cells or a multicomponent blood transfusion within 24 h following birth because of postpartum haemorrhage (≥1000 mL blood loss). Women were selected from transfusion databases and birth registries of participating hospitals. For the present analysis we selected all women with *persistent postpartum haemorrhage* [3,26].

Persistent postpartum haemorrhage was defined as postpartum haemorrhage refractory to first-line measures to control bleeding [3]. This definition is a pragmatic definition of severe postpartum haemorrhage that considers haemorrhage as severe as soon as initial measures fail to stop haemorrhage. With this definition we selected only women with ongoing postpartum haemorrhage, irresponsive to initial therapy. First-line therapies were uterine massage, continuous intravenous oxytocin, misoprostol, methylergometrine, manual placenta removal and inspection of genital tract and uterine cavity as first-line therapy in case of uterine atony, retained placenta, genital tract trauma, placenta previa or placental abruption as primary cause of postpartum haemorrhage. If a woman had multiple causes of postpartum haemorrhage, three authors (DH, KB, JvdB) determined primary cause by carefully reviewing the haemorrhage and discussion until consensus. Women with clinically abnormally invasive placenta as primary cause of postpartum haemorrhage, a surgical cause (including uterine rupture) or a congenital or acquired coagulation disorder were regarded as having persistent postpartum haemorrhage irrespective of the firstly applied therapy, as these complex haemorrhages require a series of therapeutic measures to control bleeding.

Women with unknown total volume of resuscitation fluids and women in whom fluid resuscitation with clear fluids was started after a red-cell transfusion were excluded.

Approval and a waiver of informed consent was obtained from the Medical Ethics Research Committee of the Leiden University Medical Center (P12.273), and from the institutional review board of each study centre. The study was registered in the Netherlands Trial Registry (NTR 4079).

Data collection

In the Netherlands, the course and management of obstetric emergencies are carefully recorded in medical files facilitating reconstruction of obstetric emergencies for different purposes. Detailed information concerning pregnancy, birth and course of bleeding was gathered retrospectively from routinely collected medical information. Comprehensive chart reviews were performed by well-trained medical students and research nurses. We checked all data for completeness and inconsistencies, and whenever necessary, on-site chart review was repeated.

Data included mode of birth, primary cause of haemorrhage, total volume crystalloids and colloids and time of administration, consecutive estimates of blood loss and time of estimations, blood pressure and heart rate and time of measurements, time of transfusions and time of obstetric and haemostatic interventions to control bleeding.

Outcomes

Women were followed until end of bleeding. Outcome parameters were total blood loss and adverse maternal outcome. Adverse maternal outcome was a composite of maternal mortality and severe maternal morbidity, with the latter defined as hysterectomy, arterial embolisation, or intensive care unit admission.

Clear fluids

Volume of clear fluids consisted of total volume of crystalloids and total volume of colloids administered prior to transfusion of red cells. During the study period, both crystalloid and colloid fluids were used in the Netherlands as resuscitation fluids in women with postpartum haemorrhage, at the treating physician's discretion.

We categorized women into predefined groups according to volume of clear fluids. Women who received ≤2 L of clear fluids formed the reference category, and we determined the effect of every additional litre of clear fluids on maternal outcome: >2 to ≤3 L of clear fluids, >3 to ≤4 L, >4 to ≤5 L, and, >5 to ≤7 L. We excluded women with total volume of clear fluids > 7 L.

Baseline blood loss, bleeding rate and signs of haemorrhagic shock

As the first obstetric intervention to control bleeding generally occurs simultaneously with the start of fluid resuscitation we defined *baseline* as the moment of diagnosis of *persistent postpartum haemorrhage* (Fig. S1) [3]. Depending on the patients' and bleeding characteristics, this first obstetric intervention is usually employed between 500 and 1000 mL of blood loss. For women with abnormally invasive placenta, surgical cause or coagulation disorder as primary cause of postpartum haemorrhage, baseline was set at time of birth.

To enable adjustment for *severity of haemorrhage* we quantified three variables at baseline: volume of blood loss, rate of bleeding and presence of haemorrhagic shock. Volume of blood loss during postpartum haemorrhage had been measured regularly during haemorrhage by weighing all gauzes, cloths and surgical swabs and suction into canisters. We estimated volume of blood loss at baseline with linear interpolations between observed volumes of blood loss. Rate of bleeding at baseline was calculated by dividing the volume of blood loss between the two nearest observed

measurements by the time between those measurements. Haemorrhagic shock was considered present with one measurement of systolic blood pressure ≤90 mmHg and/or a heart rate ≥120 bpm birth [27].

Statistical analyses

We used regression analyses to quantify the association between volume of clear fluids and total blood loss, maternal mortality and severe maternal morbidity. Multivariable models adjusted for the predefined potential confounders preeclampsia (yes/no), mode of birth (vaginal/caesarean), primary cause of haemorrhage (categories: uterine atony, retained placenta, abnormally invasive placenta, other), baseline blood loss (categories: <1.0 L, ≥1.0 to <2.0 L, ≥2.0 L), baseline bleeding rate (<1.0 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), and signs of haemorrhagic shock at baseline (yes/no).

Missing data in confounding variables were imputed using multiple imputation to minimize the risk of bias because of these missing data [28,29]. We included confounding variables, outcome parameters and parameters associated with the missing variables as predictive variables in the imputation models.

To assess whether our findings were robust we performed the following sensitivity analyses: analyses with categorization of women in quintiles of clear fluids volume, analyses among women with high volumes of blood loss, high bleeding rates and with signs of haemorrhagic shock present at baseline, analyses after excluding women in whom the need of red blood cells transfusion could have been predicted prior to onset of haemorrhage (i.e. women with abnormally invasive placenta), and analyses after excluding women that were treated with neuraxial blockade during labour, as in the Netherlands vascular loading with crystalloids prior to neuraxial blockade is common practice. For all sensitivity analyses we adjusted for the same confounding variables as in the main analyses.

Results

Patients

We assessed 270,101 deliveries during the study period. A total of 1391 women (0.51%) received a transfusion of at least four units of packed red blood cells or a multicomponent blood transfusion, and 1260 (0.47%) women were classified as having persistent postpartum haemorrhage (Fig. 1). A total of 377 women were excluded due to incomplete data on volume of crystalloids and colloids (n = 340), start of administration of clear fluids after start of packed red blood cells transfusion (n = 10), or clear fluids volume > 7 L (n = 27).

All 883 women received a combination of crystalloids and colloids for resuscitation. Median volume of crystalloids was 2.0 L (interquartile range, IQR 1.0–3.0), and of colloids 1.0 L (1.0–1.5).

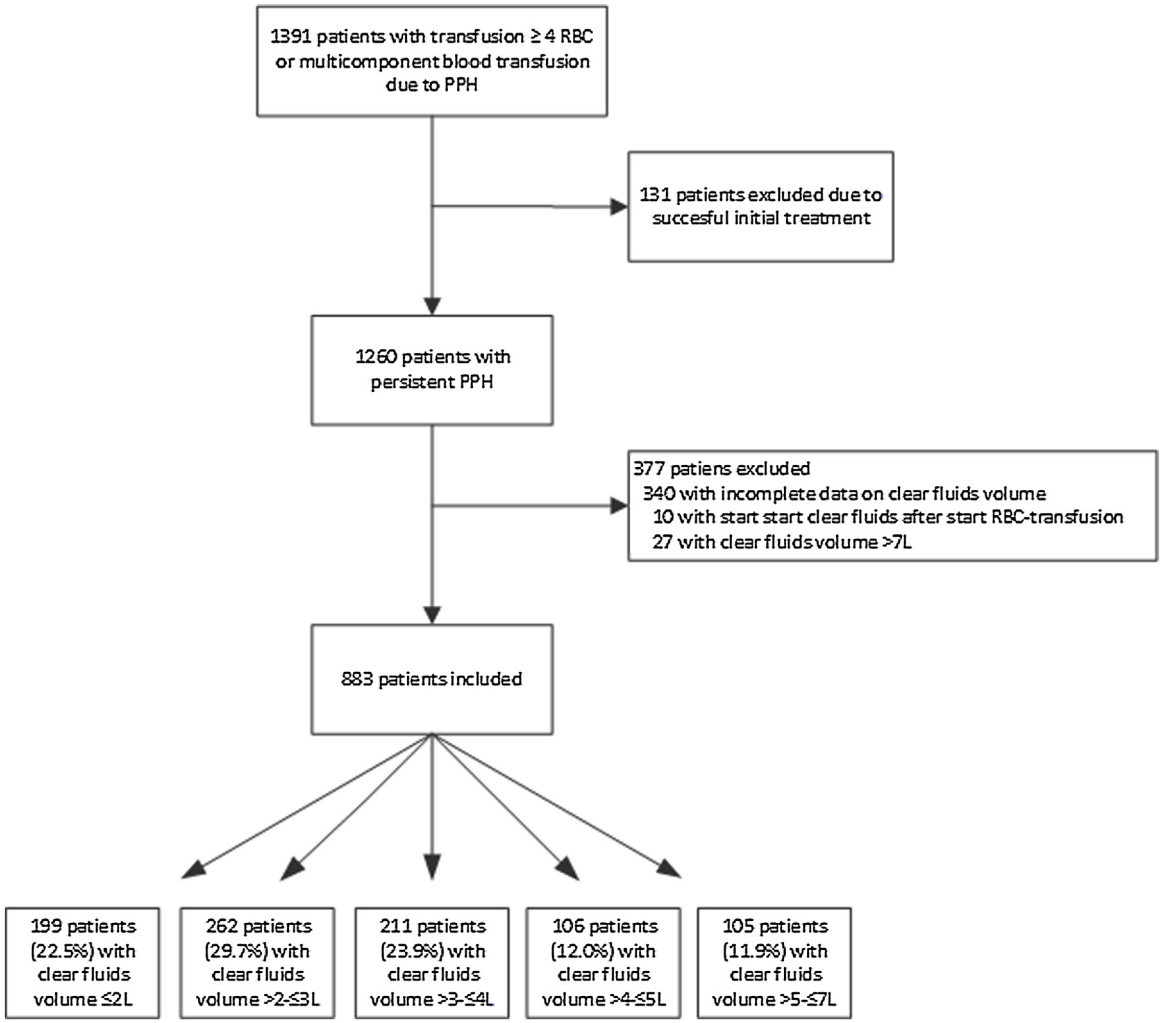

Fig. 1. Overview of included women and clear fluids volume categories.
RBC denotes packed red blood cells, PPH denotes postpartum haemorrhage.

Table 1
Demographic and pregnancy characteristics of included women with persistent postpartum haemorrhage.

Characteristic	Clear fluids volume ≤2 L[a](N = 199)	Clear fluids volume >2 to ≤3L (N = 262)	Clear fluids volume >3 to ≤4 L (N = 211)	Clear fluids volume >4 to ≤5 L (N = 106)	Clear fluids volume >5 to ≤7 L (N = 105)
Age – no. (%)					
<35 years	142 (71.4)	197 (75.2)	161 (76.3)	77 (72.6)	78 (74.3)
≥35 years	56 (28.1)	65 (24.8)	50 (23.7)	29 (27.4)	27 (25.7)
Unknown	1 (0.5)	–	–	–	–
Ethnicity – no. (%)					
Caucasian	143 (71.9)	178 (67.9)	151 (71.6)	83 (78.3)	82 (78.1)
Other/unknown	56 (28.1)	84 (32.1)	60 (28.4)	23 (21.7)	23 (21.9)
BMI – no. (%)					
<25 kg/m^2	101 (51.8)	136 (51.9)	132 (62.6)	57 (53.8)	56 (53.3)
≥25–30 kg/m^2	34 (17.1)	51 (19.5)	31 (14.7)	19 (17.9)	21 (20.0)
≥30 kg/m^2	17 (8.5)	23 (8.8)	20 (9.5)	12 (11.3)	12 (11.4)
Unknown	45 (22.6)	52 (19.8)	28 (13.3)	18 (17.0)	16 (15.2)
Preeclampsia – no. (%)	27 (13.6)	29 (11.1)	15 (7.1)	6 (5.7)	14 (13.3)
Mode of birth – no. (%)					
Vaginal	156 (78.4)	209 (79.8)	175 (82.9)	82 (77.4)	75 (71.4)
Caesarean	41 (20.6)	52 (19.8)	34 (16.1)	23 (21.7)	30 (28.6)
Unknown	2 (1.0)	1 (0.4)	2 (0.9)	1 (0.9)	–
Cause of haemorrhage – no. (%)					
Uterine atony	117 (58.8)	171 (65.3)	144 (68.2)	72 (67.9)	83 (79.0)
Retained placenta	43 (21.6)	49 (18.7)	31 (14.7)	17 (16.0)	7 (6.7)
Abnormally invasive placenta	30 (15.1)	24 (9.2)	17 (8.1)	7 (6.6)	6 (5.7)
Surgical	5 (2.5)	15 (5.7)	17 (8.1)	7 (6.6)	8 (7.6)
Other[b]	4 (2.0)	3 (1.1)	2 (0.9)	3 (2.8)	1 (1.0)

[a] Reference category.
[b] Includes placenta previa, placental abruption and congenital or acquired coagulation disorders.

Table 2
Bleeding characteristics at time of diagnosis of persistent postpartum haemorrhage and details of fluid resuscitation.

Characteristic	Clear fluids volume ≤2 L[a](N = 199)	Clear fluids volume >2 to ≤3 L (N = 262)	Clear fluids volume >3 to ≤4 L (N = 211)	Clear fluids volume >4 to ≤5 L (N = 106)	Clear fluids volume >5 to ≤7 L (N = 105)
Blood loss at baseline[b] – no. (%)					
<1.0 L	108 (54.3)	145 (55.3)	108 (51.2)	59 (55.7)	56 (53.3)
≥1.0 to <2.0 L	66 (33.2)	77 (29.4)	79 (37.4)	30 (28.3)	34 (32.4)
≥2.0 L	22 (11.1)	40 (15.3)	24 (11.4)	17 (16.0)	15 (14.3)
Unknown	3 (1.5)	–	–	–	–
Bleeding rate at baseline[b] – no. (%)					
<1.0 L/hr.	86 (43.2)	123 (46.9)	81 (38.4)	43 (40.6)	41 (39.0)
≥1.0 to <2.0 L/hr.	55 (27.6)	60 (22.9)	56 (26.5)	21 (19.8)	28 (26.7)
≥2.0 L/hr.	55 (27.6)	79 (30.2)	74 (35.1)	42 (39.6)	36 (34.3)
Unknown	3 (1.5)	–	–	–	–
Signs of haemorrhagic shock at baseline[b] – no. (%)					
No	82 (41.2)	121 (46.2)	95 (45.0)	36 (34.0)	49 (46.7)
Yes	57 (28.6)	79 (30.2)	66 (31.3)	43 (40.6)	36 (34.3)
Unknown	60 (30.2)	62 (23.7)	50 (23.7)	27 (25.5)	20 (19.0)
Type of clear fluid – L, median (interquartile range)					
Crystalloids	1.0 (0.5–1.0)	1.5 (1.5–2.0)	2.5 (2.0–3.0)	3.0 (3.0–3.5)	4.0 (4.0–4.5)
Colloids	1.0 (0.5–1.0)	1.0 (1.0–1.5)	1.5 (1.0–1.5)	1.5 (1.0–1.5)	1.5 (1.5–2.0)
Time from baseline until first unit of red blood cells - no (%)					
<1 hour	50 (25.1)	75 (28.2)	56 (26.5)	32 (30.2)	40 (38.1)
≥1 to <3 hours	91 (45.7)	124 (47.3)	109 (51.7)	53 (50.0)	47 (44.8)
≥3 hours	51 (25.6)	64 (24.4)	44 (20.9)	20 (18.9)	19 (17.1)
Unknown	7 (3.5)	–	2 (0.9)	1 (0.9)	–

[a] Reference category.
[b] Baseline was defined as time of diagnosis of persistent postpartum haemorrhage.

Table 3
Total blood loss and maternal outcomes.

Outcome	Clear fluids volume ≤2 L (N = 199)	Clear fluids volume >2 to ≤3L (N = 262)	Clear fluids volume >3 to ≤4 L (N = 211)	Clear fluids volume >4 to ≤5 L (N = 106)	Clear fluids volume >5 to ≤7 L (N = 105)
Median total blood loss (IQR) – L	2.9 (2.2 to 3.4)	3.0 (2.3 to 3.5)	3.0 (2.5 to 4.0)	3.4 (2.7 to 4.0)	4.0 (3.5 to 5.2)
Mean difference from reference group (95% CI)	ref.	0.2 (-0.1 to 0.5)	0.4 (0.1 to 0.8)	0.6 (0.2 to 1.0)	2.0 (1.6 to 2.4)
Adjusted mean difference from reference group (95% CI)[a]	ref.	0.2 (-0.1 to 0.5)	0.4 (0.1 to 0.7)	0.6 (0.5 to 0.7)	1.9 (1.5 to 2.3)
Adverse maternal outcome – no. (%)[b]	52 (26.1)	69 (26.3)	61 (28.9)	41 (38.7)	64 (61.0)
Maternal mortality – no. (%)	1 (0.5)	1 (0.4)	–	–	2 (1.9)
Hysterectomy – no. (%)	3 (1.5)	7 (2.7)	9 (4.3)	4 (3.8)	13 (12.4)
Arterial embolization – no. (%)	17 (8.5)	24 (9.2)	23 (10.9)	14 (13.2)	31 (29.5)
ICU-admission – no. (%)	46 (23.1)	55 (21.0)	51 (24.2)	35 (33.0)	52 (49.5)
Crude OR (95% CI)	1	1.0 (0.7 to 1.5)	1.2 (0.7 to 1.8)	1.8 (1.1 to 2.9)	4.4 (2.7 to 7.3)
Adjusted OR (95% CI)[a]	1	1.0 (0.7 to 1.6)	1.2 (0.8 to 1.9)	1.8 (1.1 to 3.1)	4.4 (2.6 to 7.5)
Summary of sensitivity analyses in women with the most severe haemorrhages[c]					
Baseline blood loss ≥ 1 L (N = 404)	N = 88	N = 117	N = 103	N = 47	N = 49
Crude OR (95% CI)[a]	1	1.0 (0.6 to 1.6)	1.2 (0.8 to 1.9)	1.7 (1.0 to 2.9)	4.7 (2.8 to 8.1)
Adjusted OR (95% CI)[a]	1	0.8 (0.4 to 1.5)	1.2 (0.6 to 2.4)	1.4 (0.6 to 3.3)	3.9 (1.8 to 8.5)
Baseline bleeding rate ≥ 1 L/hr. (N = 506)	N = 110	N = 139	N = 130	N = 63	N = 64
Crude OR (95% CI)[a]	1	1.3 (0.7 to 2.3)	1.3 (0.7 to 2.3)	3.0 (1.6 to 5.9)	5.4 (2.8 to 10.5)
Adjusted OR (95% CI)[a]	1	1.3 (0.7 to 2.4)	1.4 (0.8 to 2.6)	3.1 (1.5 to 6.2)	5.9 (2.8 to 12.1)
Signs of haemorrhagic shock present at baseline (N = 281)	N = 57	N = 79	N = 66	N = 43	N = 36
Crude OR (95% CI)[a]	1	0.9 (0.4 to 1.9)	1.2 (0.5 to 2.5)	2.2 (0.9 to 5.0)	5.7 (2.3 to 14.2)
Adjusted OR (95% CI)[a]	1	1.0 (0.4 to 2.2)	1.2 (0.5 to 2.7)	2.2 (0.9 to 5.4)	5.8 (2.2 to 15.7)

IQR denotes interquartile range; 95% CI denotes 95% confidence interval; ICU denotes intensive care unit; OR denotes odds ratio.
[a] Adjusted for: preeclampsia (yes/no), mode of birth (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta, or other), blood loss at baseline (<1.0 L, ≥1.0 to <2.0 L, ≥2.0 L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock at baseline (yes/no).
[b] Multiple endpoints per patient possible.
[c] Full results shown in Tables S7–S10.

Baseline characteristics of the women are depicted in Table 1. Pregnancy was complicated by preeclampsia in 13.6% of women, 20.6% of women underwent a caesarean section, and postpartum haemorrhage was predominantly caused by uterine atony (58.8%). At baseline, median blood loss and bleeding rate were 0.9 L (0.2–1.6) and 1.2 L/hr. (0.6–2.4) (Table 2). Signs of haemorrhagic shock at baseline were present in 32.1% of women, with missing data in 219 women (24.8%). Median time from baseline until the first red-cell transfusion was 100 min (50–170), similarly distributed across all clear fluids volume categories (Table 2).

Baseline characteristics of women excluded due to incomplete data on clear fluids volume were similar to characteristics of included women (Tables S1–S2).

Total blood loss

Median blood loss for all women was 3.0 L (IQR 2.5–4.0 L), and for women that received ≤2 L of clear fluids 2.9 L (2.2–3.4). Adjusted mean difference in blood loss compared with the reference group was +0.2 L (CI −0.1 to 0.5) for women in the >2 to ≤3 L category, +0.4 L (0.1 to 0.7) for the >3 to ≤4 L category, +0.6 L (0.5–0.7) for the >4 to ≤5 L category, and +1.9 L (1.5–2.3) for the highest volume of clear fluids category (Table 3).

Adverse maternal outcome

Four maternal deaths were observed in the 883 women. Arterial embolization was performed in 109 women (12.3%), and hysterectomy in 36 women (4.1%). Admission to an intensive care unit was necessary in 239 women (27.1%). Adverse maternal outcome occurred in 32.5% of the study population (n = 287).

Table 3 presents the association between volumes of clear fluids, consisting of crystalloid and colloid fluids, and adverse maternal outcome. Women who received >4 L of crystalloids and colloids suffered more adverse maternal outcomes than women in the reference group. Odds ratios (OR) for adverse maternal outcome after adjustment for confounding were for women in the >2 to ≤3 L clear fluids category 1.0 (CI 0.7–1.6), for the >3 to ≤4 L clear fluids category 1.2 (0.8–1.9), for the >4 to ≤5 L clear fluids category 1.8 (1.1–3.1) and for the >5 to ≤7 L clear fluids category 4.4 (2.6–7.5) (Fig. 2).

Sensitivity analyses

Sensitivity analyses showed similar adjusted mean differences in blood loss from the reference group and similar odds ratios for adverse maternal outcome (Tables S3–S12).

Comment

Principal findings

In this multicentre cohort study among 883 consecutive women with persistent postpartum haemorrhage, resuscitation with >4 L clear fluids was associated with subsequent bleeding and accompanying adverse maternal outcome. This association was observed within all strata of severity of bleeding.

Current knowledge

The Royal College of Obstetricians and Gynaecologists recommends crystalloids and colloids up to 3.5 L before start of blood transfusion [30]. Thus far, this recommendation was based on expert opinion and not supported by clinical quantitative evidence.

To the best of our knowledge this is the first study reporting on the association between high volumes of clear fluids and subsequent adverse maternal outcome among women with severe postpartum haemorrhage. Previous studies showed that haemodilution can lead to impaired thrombin generation and fibrin clot formation, which has been called dilutional coagulopathy [14–16].

The effects of volumes of fluid resuscitation have been studied in non-pregnant trauma patients with massive haemorrhage.

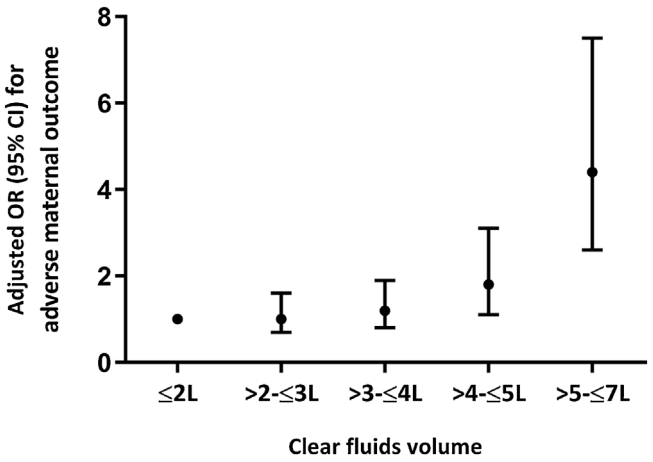

Fig. 2. Adjusted odd ratios for adverse maternal outcome plotted against clear fluids volume categories.
Adjustments for preeclampsia, mode of birth, primary cause of haemorrhage, baseline blood loss, bleeding rate and signs of haemorrhagic shock. OR denotes odds ratio, CI denotes confidence interval.
*Reference category.

Results of these studies are conflicting, and consequently, there is no consensus for trauma patients [24,25,31]. Fluid volumes of 20 L were administered, fluid resuscitation was guided by systolic blood pressures and haematocrit levels, and pregnancy was generally an exclusion criterion. A recent observational study compared crystalloid resuscitation <2 L in 1282 trauma patients with uncontrolled haemorrhage with crystalloid resuscitation ≥2 L in 289 patients [32]. Adjusted mortality was almost 2-fold higher in the high-volume patients compared with the low-volume patients. The alterations in coagulation due to pregnancy hamper translation of the results of these studies to postpartum haemorrhage.

Strengths and limitations

In this large cohort of consecutive women with persistent postpartum haemorrhage, we included women at risk of haemodilution due to resuscitation with clear fluids. To achieve this we defined persistent postpartum haemorrhage as recently proposed by an international expert panel [3]. This enabled identification of women truly at risk of progression from mild to severe haemorrhage, morbidity and mortality. Refractoriness to first-line therapy is also a clear and recognizable transition point in management of women with postpartum haemorrhage, and thus, findings of this study have direct clinical relevance for the management of women with postpartum haemorrhage.

We carefully adjusted our results for confounding. One of the most important confounders in research on management of postpartum haemorrhage is severity of haemorrhage. We adjusted for cause of haemorrhage, blood loss, bleeding rate and signs of haemorrhagic shock at baseline as proxies for severity of haemorrhage. Yet, we cannot rule out residual confounding. However, given that sensitivity analyses among women in the worst clinical condition at start of fluid resuscitation showed similar results, we feel confident to infer that resuscitation with >4 L clear fluids before start of red cell transfusion does not seem to be beneficial for these women. In contrast, it may worsen clinical outcome of women with persistent postpartum haemorrhage. Moreover, red-cell transfusions were initiated in similar timeframes across all five clear fluids volume categories, indicating similar severity of postpartum haemorrhage between groups at baseline.

Colloid fluids are expected to have a different effect on maternal outcomes because of their additional association with impaired coagulation [16,17]. Unfortunately, stratification based on type of clear fluid was not possible in our study.

To optimise adjustment for confounding we aimed to collect sequential information on blood loss and vital signs at relevant time points during ongoing postpartum haemorrhage, and cautiously reconstructed the course of bleeding in every woman. Loss to follow up did not occur because information from start till end of bleeding was available for all women, including all interventions and outcomes. As expected, we had missing data on signs of haemorrhagic shock in almost 25% of women, distributed across all categories of clear fluids volume. These missing values were imputed by using all available data on blood pressures and heart rates throughout the bleeds. It has been shown that multiple imputation is a better solution than complete case analysis in case of missing data [28].

In the Netherlands, there is a 24/7 availability of arterial embolisation in most hospitals, and this intervention is performed before resorting to hysterectomy. This may explain our relatively high embolisation and low hysterectomy rate.

Clinical implications

Our findings suggest that fluid resuscitation with clear fluids becomes clinically relevant in women with persistent postpartum haemorrhage when clear fluids volume exceeds 4 L, within all strata of severity of bleeding. Consequently, clinicians should switch to red-cell transfusion before reaching this 4 L limit of clear fluids in women with ongoing postpartum haemorrhage, in order to prevent adverse maternal outcome associated with high clear fluids volume.

Authors' contributions

DH, KB, JZ, JR, JJZ and JvdB were responsible for study concept and design. DH monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data. RM collected data and helped development of the data collection tool. DH and JvdB drafted and revised the paper. KB, JZ, JR and JJZ critically reviewed the manuscript and approved the final version. All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analyses.

Data statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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