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FLUID RESUSCITATION AND POSTPARTUM HAEMORRHAGE

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1

General Introduction

INTRODUCTION

This thesis is aimed at providing building bricks for a more evidence-based approach to the clear fluid resuscitation policy in women with postpartum haemorrhage. In the present introduction, we will first provide background information on postpartum haemorrhage (PPH), the incidence of PPH, and risk factors contributing to PPH. Subsequently we will outline the management of PPH and current guidelines and describe the normal maternal physiological changes during pregnancy. Next, we will give background information on thromboelastometry and its role within the obstetric field. We will close this chapter with an outline of this thesis.

POSTPARTUM HAEMORRHAGE

Globally, postpartum haemorrhage is one of the leading causes of maternal morbidity and mortality. Internationally, PPH is defined as more than 500 to 1000 mL blood loss in the first 24 hours after delivery.[1-4] Its definition differs between countries. Some countries differentiate between vaginal delivery (more than 500 mL) and caesarean delivery (more than 750 to 1000 mL).[2] In the Netherlands, PPH is defined as more than 1000 mL in the first 24 hours after vaginal or caesarean delivery.[5] Irrespective of the differences in definition, the overall incidence of PPH is rising in the developed countries.[2, 6-8]

In the Netherlands the overall incidence of PPH in singleton deliveries was 5.4% between 1999 and 2009.[9] Incidence increased from 4.1% in 2000 to 6.4% in 2013.[10] Since then, the incidence of PPH in the Netherlands stabilized, with a mean incidence of 6.2% in 2020.[11] The increase in the incidence of PPH as observed in the Netherlands is seen in other developed countries as well. In Sweden, the incidence of PPH increased from 5.4% in 2000 to 7.3% in 2016, a relative increase of 37%.[12] In Australia, the incidence of PPH increased from 6.1% in 2003 to 8.3% in 2011.[7] In a study across multiple developed countries, Knight *et al.* reported an overall increasing incidence varying from 4-5% in 1991 to 5-7% in 2005.[2]

RISK FACTORS AND CAUSES OF POSTPARTUM HAEMORRHAGE

Risk factors for PPH include: prior PPH, prolonged labour, induction of labour, mode of delivery (operative vaginal delivery, caesarean delivery with or without labour), previous caesarean delivery, increased maternal age, hypertensive disorders of pregnancy, diabetes mellitus, coagulation disorders, polyhydramnios, chorioamnionitis, multiple gestation, uterine fibroids, and placental adherence problems.[2, 6, 13, 14]

Causes of PPH can be grossly divided into 4 main categories known as 'the four Ts' [15]:

- Tone (atony)
- Tissue (retained placenta or placental remnants)
- Trauma (of the genital tract)
- Thrombin (coagulation disorders, pre-existing or acquired)

Uterine atony, in which the uterus does not contract sufficiently and the vessels in the placental bed are not compressed, accounts for over 70% of cases. Uterine atony thus constitutes the leading cause of PPH. The second most prominent cause of PPH is genital trauma.[13, 15]

Risk factors such as increased maternal age, induction of labour, operative mode of delivery, multiple pregnancy and hypertensive disorders, are increasing in developed countries, but cannot explain the increasing rates of PPH.[2, 12] Four retrospective studies performed in the USA, Australia, and Canada concluded that a correction for changes in risk factors and protective factors did not alter the increasing trend.[6, 14, 16, 17] Uterine atony remains the increasing and leading cause for PPH.[6] The share of non-atonic causes in PPH such as placental remnants and coagulation, remained stable throughout the years.[6, 14, 16]

MANAGEMENT OF POSTPARTUM HAEMORRHAGE AND CURRENT GUIDELINES

A new evidence-based guideline for the management of PPH was introduced by the Dutch Society of Obstetrics and Gynaecology (NVOG) in 2003. The guideline was disseminated through Dutch hospitals, and was updated in 2013-2015. Alongside the new guideline, the MOET (Managing Obstetric Emergencies and Trauma) course was rolled out as a nationally recommended course.[15] However, despite the introduction of both the new guideline and MOET course, an increase in the incidence of PPH was seen.[18] Evidently, the understanding of the contributing factors for PPH is not yet sufficient, and it is worthwhile to explore other contributing factors and to evaluate the current advised protocols for managing PPH.

Management of PPH consists of a combination of treatments with uterotonics, intervention surgery, coagulation support, and resuscitation with clear fluids and blood products. All treatments aim to resolve the cause of the bleeding, whilst keeping the parturient haemodynamically stable. Although research on the use of uterotonic medication is extensive, less evidence is available for optimal fluid resuscitation management.[19] At the start of the project described in this thesis, no evidence from prospective research in the obstetric field was available on the interaction of fluid resuscitation, its progression of PPH and its effect on coagulation. Gillissen *et al.* and Henriquez *et al.* published retrospective findings supporting the effect of fluid resuscitation on coagulation in severe PPH.[20, 21]

Both the Royal College of Obstetricians and Gynaecologists (RCOG) and the Managing Obstetric Emergencies and Trauma course (MOET) advise generous volume resuscitation to restore blood volume and oxygen carrying capacity: about twice the volume lost and up to 3.5 L of fast fluid infusion in those with more than 1000 mL bloods loss or signs of clinical shock.[4, 15] The American College of Obstetricians and Gynaecologists (ACOG) advises preparations for blood transfusion in women with more than 1500 mL blood loss or in women with abnormal vital signs such as hypotension and tachycardia. This practice bulletin does not mention clear fluid resuscitation.[22] Dutch guidelines advise to start volume resuscitation in case of profuse blood loss, not quantifying a minimum amount of blood loss. The Dutch guideline states there is currently no evidence to support administering more fluids than lost.[5, 23] This advice however, was given after the start of our current study.

VOLUME RESUSCITATION

Volume resuscitation with crystalloids, colloids and blood products all have their own advantages and disadvantages. Crystalloids are isotonic and designed to replace losses within in the extracellular compartments therefore requiring large amounts when used to replace intravascular losses.[24] Infusion of large amounts of crystalloids may induce acidosis, dilutional coagulopathy, formation of interstitial oedema and impairment of the microcirculation which can lead to the lethal triad of acidosis, hypothermia, and coagulopathy.[25, 26] Colloids such as hydroxyethyl starches designed to replace plasma deficits, may impair clot formation and lead to faster clot disintegration.[24] Infusing a large amount of colloids can disrupt the haemostasis and as such actually increase the bleeding.[27-29] Blood products will replace the lost coagulation factors, but are a scarce commodity and are not without risks for, among other things, future pregnancies and possible irregular antibody formation.

OTHER MEDICAL FIELDS

Until recently, high volume strategies were advocated to reverse haemorrhagic shock. This strategy has been the gold standard worldwide since 1960s, even though prospective randomised trials were lacking at its introduction.[26, 30] Some studies outside the obstetric field, performed in animals, military settings, and non-pregnant women, indicate that aggressive fluid resuscitation may in fact *worsen* the haemorrhagic shock, and advise a more restrictive approach. Overall, these studies show an advantage for a more restrictive approach in regard to the 'lethal triad', survival rate, less progression of total blood loss and less blood transfusion needed.[31-34] Unfortunately, as pregnant women undergo specific cardiovascular and haematologic changes, these results cannot be directly applied to pregnant women during labour.

Other studies found no clear advantage or even disadvantage for a restrictive approach, such as an increased risk for kidney failure.[35-37] Concerns about a restrictive policy include a possible reduced oxygen delivery capacity, and hypotension which can result in inadequate tissue perfusion and therefore organ failure. Overall, the trials are underpowered and contradictory, which is reflected in the guidelines of the American Society of Anesthesiologists (ASA)[24, 38, 39] and the European Society of Anaesthesiology (ESA).[40-42] The ASA guideline stipulates disagreement on the matter, and states that the optimal regimen is to replace losses. In their guideline, ESA warns to avoid hypoperfusion and advises a goal-directed approach during surgery.

MATERNAL PHYSIOLOGICAL CHANGES DURING PREGNANCY

Cardiovascular changes

During pregnancy, numerous unique adaptations accommodate the growing foetus in anticipation of delivery. These adaptations are seen as early as six weeks into gestation.[43, 44] Plasma volume increases by 30-50%, increasing the preload of the cardiac system. Because of vasodilation the afterload is reduced. As part of the cardiovascular changes, the systemic vascular resistance decreases and with it the blood pressure. Blood pressure slightly increases again at term.[43, 44] Cardiac output increases by 30-50% due to an increase in stroke volume of 20-30%, and an increase in maternal heartrate by 15-20 beats per minute.[43-45] Anatomically, the heart adapts to pregnancy with a more upward and more rotated position. The ventricular wall muscle mass and the valvular annular diameters are increased to accommodate for the increased stroke volume, reflecting increased cardiac compliance.[43-45] Even during labour itself, alterations occur:

cardiac output increases 15% during the first stage and 50% during second stage of labour. Directly postpartum, another 60-80% rise in cardiac output occurs mainly due to transfer of extravascular fluid returning intravascularly.[43-45] This sharp rise in cardiac output continues for about an hour postpartum, and then gradually subsides. It can take up to 24 weeks for the cardiac output to return to non-pregnant values.[43-45]

Haematologic changes

Red blood cell counts increase by 12-25%. As this rise is disproportional to the rise of 30-50% in plasma volume, pregnancy results in a dilutional anaemia.[43, 44] Expression of several clotting factors increases and coincidentally decreases for some anti-coagulants. Factors VII, VIII, X, and XII, von Willebrand factor and ristocetin cofactor increase during pregnancy. Levels of fibrinogen increase up to 200% above pre-pregnancy levels at term.[46, 47] Expression of other factors may increase or decrease slightly, or remain stable during pregnancy.[46, 47] Anticoagulant protein C and antithrombin levels remain relatively stable while protein S levels decrease during pregnancy. During pregnancy there is diminished fibrinolytic activity due to diminished tissue plasminogen (t-PA) activity.[46, 47] All these changes are most pronounced at term, with the greatest activity during placental expulsion due to the release of thromboplastic substances.[46] This hypercoagulable state should protect the parturient from bleeding excessively. Coagulation generally returns to the pre-pregnant state 3-4 weeks postpartum.[46] As haemostasis during the management of PPH is affected by dilution coagulopathy or by increased usage of coagulation factors, monitoring and potentially treatment of the coagulation capacity of the parturient with PPH is necessary.

THROMBOELASTOMETRY

Thromboelastometry (TEG) is a point of care viscoelastic test of haemostasis in whole blood. Rotational thromboelastometry (ROTEM®) evolved from TEG technology and is based upon the same principle: visual information on clot formation and strength.[48] Available tests for ROTEM® are shown in table 1. The most commonly used assays during PPH are INTEM, EXTEM, and FIBTEM.

In contrast with regular haemostasis tests, which generally take 45-60 minutes, thromboelastometry offers quick bedside information on the haemostasis and the effectiveness of the measures taken to correct the haemostasis.[48] Another advantage of thromboelastometry over conventional testing is the use of whole blood rather than plasma which gives a better representation of the whole coagulation system function rather than separate parts of the coagulation system.[49] It provides information on

thrombin formation, clot strength, fibrinolysis, platelet function, and fibrinogen function independent of platelets.[48, 49] However conventional laboratory tests can presents quantitative information on specific coagulation factors, fibrinogen, and platelets which thromboelastometry cannot.

Table 1 ROTEM® assays

ROTEM® test	Description
INTEM	Contact activation (intrinsic pathway). Provides information on coagulation factors and platelets. Similar to activated partial prothrombin time (APTT). Influenced by heparin.
EXTEM	Tissue factor activation (extrinsic pathway). Provides information on coagulation factors and platelets. Similar to prothrombin time (PT). Not influenced by heparin.
FIBTEM	Tissue factor activation. Information on fibrinogen contribution to cloth strength independent of platelets. Not influenced by heparin.
HEPTEM	Evaluates the effect of heparin on the INTEM assay.
APTEM	To asses fibrinolysis in combination with EXTEM. Helps to identify the need for antifibrinolytic drugs.
NATEM	Non-activated ROTEM, whole blood sample analysed after recalcification.

Figure 1 depicts a basic ROTEM® figure. Figure 2 and Figure 3 depict visual ROTEM® results. Even though both figures are complete ROTEM® results, the development and formation of these figures results can be viewed in real time.

Thromboelastometry has been proven to be more cost-effective in cardiothoracic surgery and trauma patients than regular haemostasis tests.[51] Both the ESA and the ASA recommend thromboelastometry in routine practice for massive non-obstetric haemorrhage. However, the "*European guideline on management of major bleeding and coagulopathy following trauma*" notes that the usefulness of viscoelastic measurements is still evaluated and therefore is unable to offer advice on the use of this method. In contrast it does state in their recommendation to include routine, early and repeated coagulation monitoring by standard assays and/or viscoelastic method.[52] In obstetrics guidelines thromboelastometry is not yet implemented. Both the RCOG and the NVOG recommend conventional laboratory testing at 500 to 1000 mL blood loss.[4, 5] Beside the current guidelines, data is scarce on the use of thromboelastometry on PPH guided treatment.[53] Most studies were (prospective) observational studies, mainly focused on fibrinogen and not published yet at the start of this thesis.[53] Overall these results seem to show benefit of thromboelastometry in the PPH care. Three are worth to highlight: Barinov

et al. concluded in a randomised controlled trial that the use of a combined haemorrhage management in caesarean sections, also including TEG, resulted in significantly lower numbers of postpartum hysterectomies, less incidence of blood loss more than 2000 mL, and lower mean total blood loss. However, the combined management also included ligation of the arterial branches and placing a balloon tamponade therefore the individual contribution of TEG alone in this management is not clear.[54] Snegovskikh *et al.* retrospectively showed women with PPH treated with a ROTEM® algorithm had significantly less transfusions, fewer hysterectomies, lower intensive care admittance, and shorter hospitalisation than those managed with a traditional protocol.[55] Bell *et al.* reported a decrease in massive red blood cell transfusion since the gradual adoption of thromboelastometry in Wales. Limitation of this observational study is the lack of control arm.[56] The role of thromboelastometry is promising in the management of PPH but has not yet unequivocally proven its use. The main advantage would be the quick turnaround time compared to conventional testing.

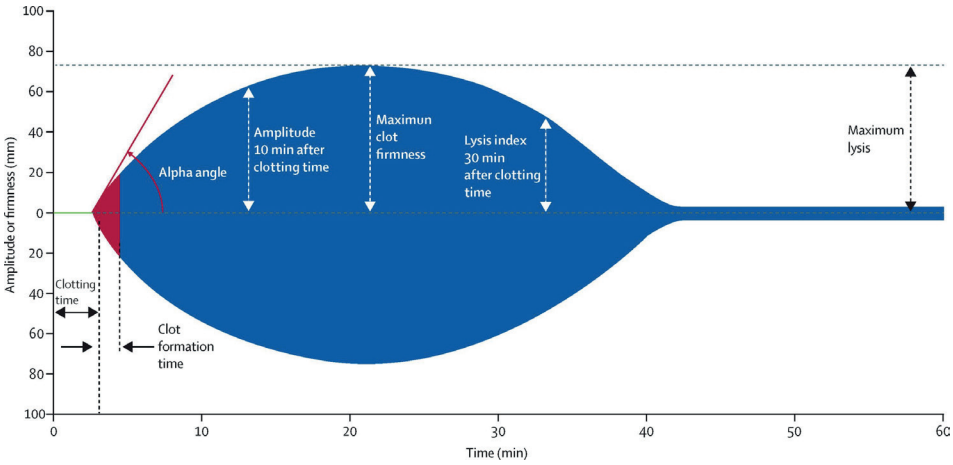

Figure 1 ROTEM® base figure

As ROTEM starts to develop, the time to start the clot formation is depicted in a green line, defined as clotting time. Magenta depicts the time it takes for the clot formation. The alpha angle is dependent on the clot formation time and the amplitude of the clot. The amplitude of the clot formed can be read at different times in the process. The maximum clot firmness is the maximum amplitude the clot reaches at any given time. The amplitude decreases in time run, giving the lysis index and maximum lysis. Depending on how soon fibrinolysis is seen, this might need to be corrected.
Figure available through creative commons CC-BY license.[50]

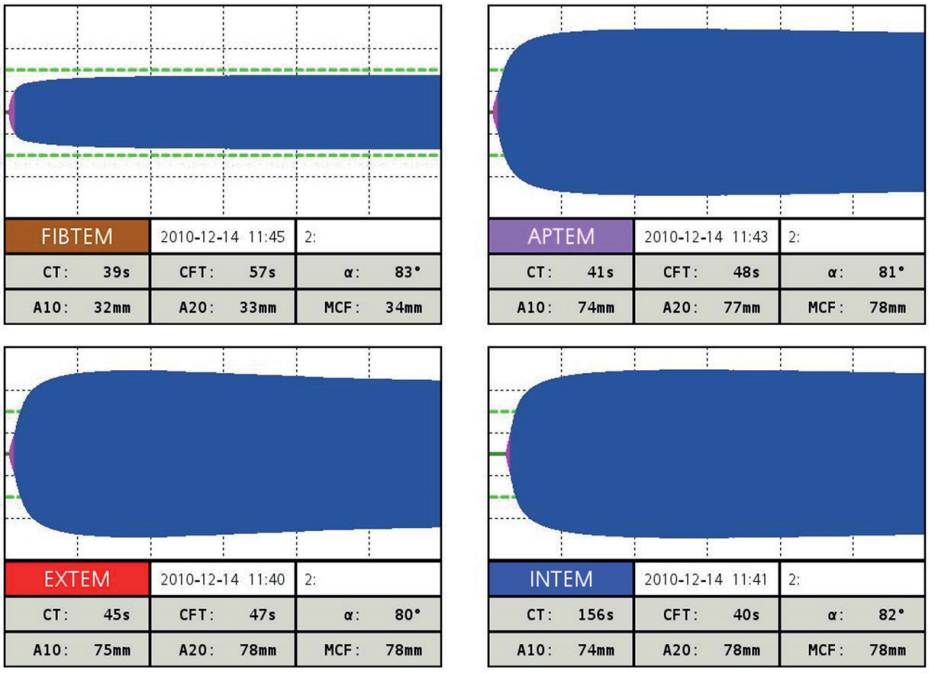

Figure 2 normal ROTEM® values

Figure 2 shows a normal coagulation status.

CT = clotting time, CFT = clot formation time, α = alpha angle, A10 = amplitude after 10 minutes, A20 = amplitude after 20 minutes, MCF = maximum clot firmness.

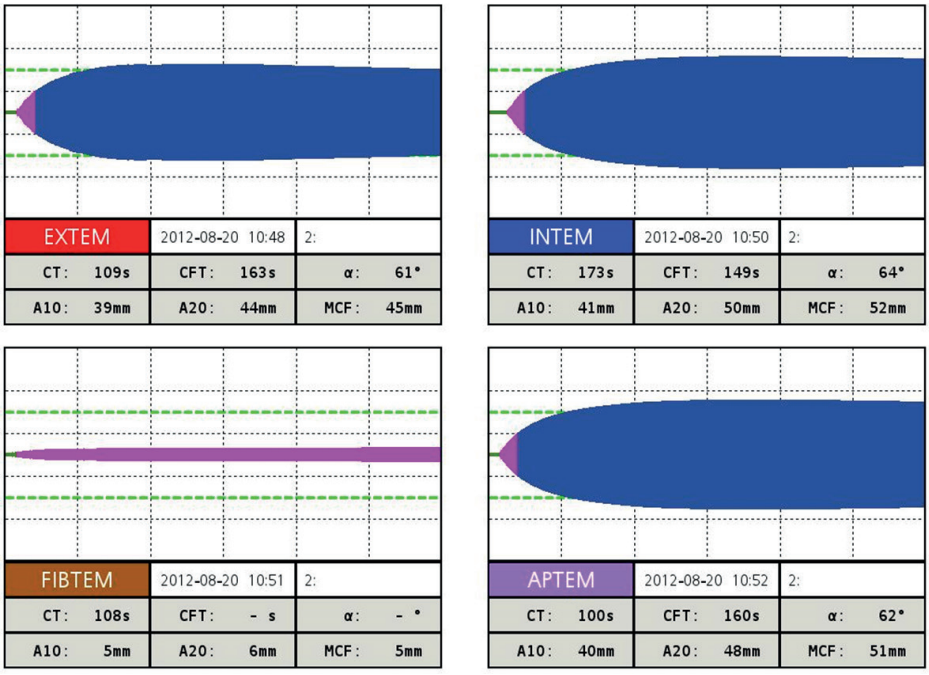

Figure 3 Abnormal ROTEM® result

This figure depicts an abnormal FIBTEM results in ROTEM® evaluation indicating the specific need for fibrinogen administration. EXTEM, INTEM, and APTEM are within normal reference values eliminating the need for packed cells, fresh frozen plasma or other blood products besides fibrinogen. CT = clotting time, CFT = clot formation time, α = alpha angle, A10 = amplitude after 10 minutes, A20 = amplitude after 20 minutes, MCF = maximum clot firmness.

THESIS AIM AND OUTLINE

The general aim of this thesis is to improve the evidence base for the care of women with postpartum haemorrhage.

The main objectives for this thesis are:

1. To evaluate the existing evidence of restrictive fluid resuscitation in other medical fields.
2. To evaluate if a more restrictive fluid resuscitation policy in postpartum haemorrhage at 500 mL reduces progression towards a severe postpartum haemorrhage (≥ 1000 mL).
3. To evaluate the prevalence of abnormal haemostasis as observed with ROTEM™ in regular postpartum haemorrhage care.
4. To evaluate the effect of a restrictive fluid resuscitation strategy on haemostatic parameters including ROTEM™ parameters.

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2

Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis

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ABSTRACT

Study Objective: This article reviews if a restrictive fluid management policy reduces the complication rate if compared to liberal fluid management policy during elective surgery.

Design: The PubMed database was explored by two independent researchers. We used the following search terms: "Blood transfusion (MESH); transfusion need; fluid therapy (MESH); permissive hypotension; fluid management; resuscitation; restrictive fluid management; liberal fluid management; elective surgery; damage control resuscitation; surgical procedures, operative (MESH); wounds (MESH); injuries (MESH); surgery; trauma patients". A secondary search in the Medline, EMBASE, Web of Science and Cochrane library revealed no additional results.

Setting: Randomised controlled trials performed during elective surgeries.

Patients: All subjects were scheduled for elective surgery. The patient characteristics and the type of surgery varied. All but three studies reported ASA groups 1-3 as inclusion criterion.

Interventions: Patients were randomly assigned to a restrictive fluid management policy or to a liberal fluid management policy during elective surgery.

Measurements: The primary outcome of interest is total number of patients with a complication and the complication rate. Secondary outcome measures are infection rate, transfusion need, postoperative rebleeding, hospital stay and renal function.

Main Results: 1397 patients were analysed (693 restrictive protocol,704 liberal protocol). Meta-analysis showed that in the restrictive group, as compared with the liberal group fewer patients experienced a complication (RR 0.65, CI 95%: 0.55-0.78). The total complication rate (RR 0.57, CI 95%:0.52-0.64), risk of infection (RR 0.62, CI 95%: 0.48-0.79) and transfusion rate (RR 0.81, CI 95% 0.66-0.99) were also lower. The postoperative rebleeding did not differ in both groups: RR 0.76 (CI 95%: 0.28-2.06).

Conclusions: Compared with a liberal fluid policy a restrictive fluid policy in elective surgery results in a 35% reduction in patients with a complication and should be advised as the preferred fluid management policy.

HIGHLIGHTS

- 35% complication reduction with a restrictive fluid policy
- Fewer infections occur when a restrictive fluid policy is adopted in elective surgery
- Fewer blood transfusions with a restrictive fluid policy in elective surgery

INTRODUCTION

Although fluid therapy is a cornerstone in current surgical practice, no consensus on the optimal perioperative fluid management exists and the existing trials are contradictory.

Since Shires in 1961 a liberal transfusion practice is advocated.[1] Today's textbook management is approximately 20 mL/kg/hour fluid transfusion (crystalloids and colloids) to account for fasting, third space and urine losses.[2] On top of the standard management, blood loss will be compensated 3-4 times the actual loss.[2] Even though a more liberal fluid management is practised widely it has never been properly evaluated.[3] Excessive fluid therapy is associated with negative outcomes, even in healthy patients (American Society of Anesthesiologists (ASA) 1).[2, 4-7] One important side effect of the liberal approach is volume overload which may cause reduced pulmonary function, postoperative reduced gut motility, and reduced subcutaneous oxygen tension.[5, 7] More fluid puts a greater demand on the cardiac and urinary system predisposing for cardiac morbidity and urinary retention.[5] Additionally the crystalloids and colloids transfused interfere with coagulation due to dilution, acidosis or faster clot disintegration.[5, 8-10]

Recently more restrictive perioperative fluid management policies have been studied in randomised controlled trials challenging the liberal practice. Despite avoiding an overloading effect, restrictive fluid management and its potential hypovolemic state are associated with impaired cardiac output. This results in inadequate oxygenation putting the organs at risk for ischemia, infarction and organ failure.[2] With all strategies having their own risks the most important goal is to achieve an optimised state with a normovolemic patient.

In this systematic review we will evaluate a liberal versus a restrictive policy intraoperatively in general elective surgery. The primary outcome of interest is total number of patients with a complication and the complication rate (defined as the total number of complications given in the trials per group). The secondary outcome measures are hospital stay, infection rate (the total of peritonitis, sepsis, wound

infection, pneumonia, urinary tract infection, and wound abscess), postoperative bleedings (defined as the total number of postoperative bleedings that occurred requiring transfusion and surgical treatment), transfusion need and renal function.

METHODS

In this systematic review, the PRISMA statement for reporting reviews was applied.[11] The PubMed database was explored by two independent researchers to identify appropriate articles. We used the following search terms: "Blood transfusion (MESH); transfusion need; fluid therapy (MESH); permissive hypotension; fluid management; resuscitation; restrictive fluid management; liberal fluid management; elective surgery; damage control resuscitation; surgical procedures, operative (MESH); wounds (MESH); injuries (MESH); surgery; trauma patients". A secondary search in the Medline, EMBASE, Web of Science and Cochrane library revealed no additional results.

Studies had to meet the following criteria to be included: (1) a randomised controlled trial, (2) a population that was admitted for any kind of elective surgery, (3) a comparison of restrictive and liberal fluid management with complication rate and/or hospital stay as outcome measurements. No restrictions were set with regard to age, ethnicity or sex. Articles were excluded if a goal directed approach of fluid management or if an additional anaesthesia was used in either of the groups (e.g. restrictive policy with epidural compared to standard care without an epidural anaesthesia) was used. Screening was done on title and abstract, if this provided insufficient information, the full text was read. Inclusion and exclusion was done independently by two researchers. Disagreement about inclusion or exclusion was resolved through discussion and a third researcher was decisive if needed. The reference lists of included articles were screened for additional articles.

The following data was extracted and summarised: (1) number of participants and type of surgery, (2) intervention protocol, (3) outcome measures and (4) results. The required data was available in all selected articles.

One researcher (I.M.T.) performed the quality assessment (appendix 1), according to the CONSORT guideline for reviewing randomised controlled trials.[12] All items were scored and given the following codes:

+ (one point) good, clearly described and taken into account
+/- (half a point) moderately well described, not entirely clear
- (zero points) bad, not described or not taken into account
N/A (not considered in the final judgment) when the item was not applicable to the study.

A meta-analysis was performed on the primary and secondary outcomes with Review Manager version 5.2. The statistic used was risk ratio. As the included studies are heterogeneous regarding surgical types, a random effects model (with Mantel-Haenszel method) was chosen.

To calculate with adverse events in percentages, we divided the total number of patients with any complication in a group by the total number of patients in that group.

RESULTS

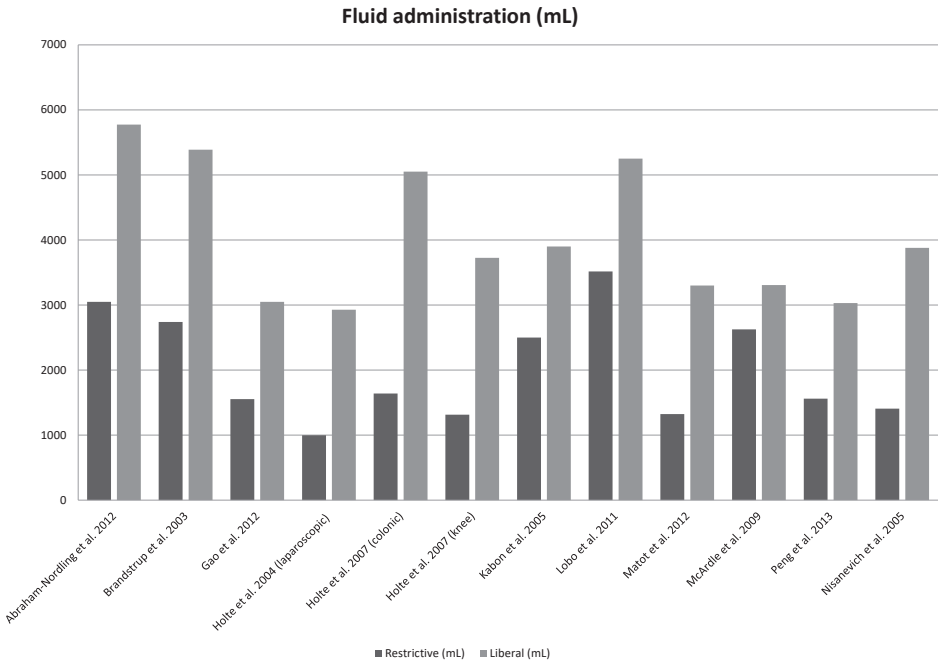
Study Selection

The two individual PubMed searches resulted in 2330 and 1692 articles. After screening on title and abstract and removing duplicates, 4003 articles were excluded. Eighteen articles remained, one of which was not accessible in full text. Two additional articles that met the eligibility criteria were found by screening the reference lists. A total of nineteen full text articles have been read. Six were excluded as they did not meet the eligibility criteria; goal directed fluid management (n = 2), the absence of a liberal group (n = 1), the absence of a restrictive group (n = 1), unclear intervention protocol (n = 2), complication rate or hospital stay were not outcome measures (n = 1). A total of twelve randomised controlled trials were included in the systematic review.[13-24]

Study Characteristics

All subjects (1397 patients were analysed (693 restrictive protocol,704 liberal protocol)) were scheduled for elective surgery. The patient characteristics and the type of surgery were heterogeneous, varying from age > 65 years and morbidly obese patients to cancer patients. All but three studies reported ASA groups 1-3 as inclusion criterion. One included all patients with an abdominal aortic aneurysm (AAA) repair[22], one did not select on specific ASA criteria but excluded on age, weight and additional diseases.[16] The third study included any elective surgery with an American College of Cardiology risk score > 3.[20] Criteria for exclusion were similar in all studies. Inclusion- and exclusion criteria are shown in table 1. The intraoperative fluid management in nine out of twelve studies consisted of Ringer's lactate.[15-21, 23, 24] Other used solutions were buffered glucose 2.5%[13], Hartman solution[22] and normal saline 0.9%.[14] All solutions used were crystalloids,

in 5 studies with addition of colloids (hydroxyethyl starch).[14, 15, 17, 18, 24] In each individual study the restrictive group received no more than the liberal group. Overall, the liberal group received more fluids compared with the restrictive group (mean 4048 mL (2928-5775 mL) versus mean 2019 mL (997.5-3517 mL) respectively, see graph 1). Total amount of complications were available in all studies with the exception of two studies.[16, 19] Other relevant outcome measures were hospital stay and renal function. An overview of study characteristics is given in table 2.



Graph 1 fluid administration per study

Results of individual studies and meta-analysis

A statistically significant difference in total number of complications within 30 days was found in 5 studies. All but one of these 5 studies showed more complications in the liberal group in comparison to the restrictive group[14, 20, 22, 23], the other one showed more complications in the restrictive group.[17] One study showed the infection rates between both groups. These results were not statistically significantly different.[19] An overview of results per trial is given in table 3.

The total number of complications was subdivided in different categories. Percentages of bleeding, wound infection, pneumonia, sepsis, cystitis and peritonitis were extracted as shown in table 3. For the exact definitions used per outcome per study see appendix 2. Percentages of bleeding, sepsis and peritonitis did not differ between the two groups. Wound infection, pneumonia and cystitis were more common in the liberal group.

Data concerning hospital stay were available in 7 studies[13, 16-19, 22, 23]: McArdle *et al.* and Nisanevich *et al.* found that the length of hospital stay was significantly lower in the restrictive group; 9 days versus 18 days (p0.010, McArdle *et al.*) and 8 versus 9 days (p0.01, Nisanevich *et al.*). While Abraham-Nordling *et al.*, Holte *et al.* (knee arthroplasty), Holte *et al.* (colonic surgery) and Kabon *et al.* found no difference. Holte *et al.* (laparoscopic) found that hospital stay was longer in the restrictive group. In the restrictive group 15/23 patients could be discharged the same day of surgery compared with 21/22 patients in the liberal group ($p < 0.03$). No data is available on the length of stay of the remaining patients.

Renal function data were available in 3 studies[14, 21, 22], however different methods were used to assess renal function. McArdle *et al.* measured the urinary albumin/creatinine ratio and found a significantly higher value (suggesting impaired renal endothelial function) in the liberal group. Brandstrup *et al.* reported a significantly lower serum creatinine in the liberal group upon arrival in the recovery room. There was no difference found in the subsequent days. In addition, Matot *et al.* found there was no significant difference between the restrictive and liberal group and that mean creatinine serum concentrations were within the reference range at all times. Furthermore, Matot *et al.* measured low urine outputs in the majority of the patients in both groups without any statistical difference between the liberal and restrictive group.

Figure 1 shows the results of meta-analysis of the primary and secondary outcome measures: total patients with a complication, the complication rate, and secondary outcome measures transfusion need, postoperative rebleeding and cumulative infection rate.

The total amount of patients with a complication is significantly higher in the liberal approach: RR 0.65 (CI 95%: 0.55-0.78). Also, the total complication rate is significantly lower in the restrictive policy group compared with the liberal policy group: RR 0.57 (CI 95%:0.52-0.64). A higher risk of infection is found and more transfusions are needed in the liberal policy group: RR_{inf}0.62 (CI 95%: 0.48-0.79) and RR_{trans}0.81 (CI 95%: 0.66-0.99). While the post-operative rebleeding did not differ in both groups: RR 0.76 (CI 95%: 0.28-2.06).

Table 1 In- and exclusion criteria

Study	Inclusion criteria
Abraham-Nordling *et al.* 2012	Admitted for elective colorectal resection, ASA groups 1-3
Brandstrup *et al.* 2003	Admitted for elective colorectal resection, ASA groups 1-3
Gao *et al.* 2012	Admitted for gastrointestinal cancer surgeries, 65 years or older, ASA 1-3
Holte *et al.* 2004 (laparoscopic)	Admitted for elective laparoscopic cholecystectomy, set up for ambulatory setting.
Holte *et al.* 2007 (colonic surgery)	Admitted for elective colonic surgery, ASA 1-3
Holte *et al.* 2007 (knee arthroplasty)	Admitted for fast-track elective primary knee arthroplasty, ASA 1-3
Kabon *et al.* 2005	Admitted for open elective colon resection with an anticipated duration of surgery greater than two hours. Age 18-80 years. ASA 1-3
Lobo *et al.* 2011	Admitted for elective surgery, American College of Cardiology risk score ≥ 3
Matot *et al.* 2012	Admitted for laparoscopic bariatric surgery, ASA 1-3
McArdle *et al.* 2009	Admitted for conventional open elective infra-renal AAA repair
Nisanevich *et al.* 2005	Admitted for major elective intra-abdominal surgery, ASA groups 1-3
Peng *et al.* 2013	Admitted for gastrointestinal surgery for malignancy, ASA groups 1-3

	Exclusion criteria
	Disseminated or secondary cancer, diabetes mellitus, renal insufficiency, alcohol overconsumption, inflammatory bowel disease, pregnancy, lactation, mental disorders, contraindication to epidural analgesia
	Disseminated cancer, diabetes mellitus, renal insufficiency, alcohol consumption of > 35 drinks/ week, inflammatory bowel disease, pregnancy, lactation, mental disorders, contraindication to epidural analgesia, secondary cancers, language problems
	Disseminated cancer, diabetes mellitus, renal insufficiency, inflammatory bowel disease, lactation, mental disorders, contraindication to epidural analgesia, secondary cancers, language problems, smoking within 2 weeks
	Weight > 100 kg, age > 70 or < 18 years, pregnancy or lactation, ongoing infection, inability to perform the preoperative test, conversion to open procedure, history of cardiovascular/ pulmonary or endocrine disease, regular intake of any medication except contraception pills/ postmenopausal oestrogen supplements/SSRIs. Operations performed in the afternoon
	Insulin-dependent diabetes mellitus, alcohol intake > 5 units daily, inflammatory bowel disease, age < 50 years, weight > 110 kg, BMI > 35, psychiatric illness, no thoracic epidural, severe cardiac of pulmonary illness.
	Insulin-dependent diabetes mellitus, alcohol intake > 5 units daily, age < 50 years, weight > 110 kg, BMI > 40, psychiatric illness, inability to perform the preoperative test program, severe cardiac or pulmonary insufficiency, glucocorticoid maintenance therapy, anticoagulant treatment, contraindication to intraoperative tranexamic acid or to epidural catheter insertion, chronic opioid use, morphine intolerance, surgery not by project surgeon
	Renal failure, congestive heart failure, recent history of fever or infection, susceptibility to malignant hyperthermia, diuretic therapy, or a history of pulmonary oedema.
	Chronic renal failure, unplanned surgery, unavailability of ICU beds, pregnancy, congestive heart failure, acute myocardial ischemia prior to enrolment, life expectancy < 60 days, palliative treatment,
	Renal dysfunction, < 18 years old, congestive heart failure, receiving diuretics
	Psychiatric illness, haematological disorder, known infection, severe cardiac or pulmonary insufficiency, emergency surgery
	< 18 years old, pregnant, congestive heart failure, hepatic or renal dysfunction, patients undergoing hepatectomy, coagulopathy
	Disseminated cancer, diabetes mellitus, renal insufficiency, mental disorders, contraindication to epidural analgesia, malnutrition.

Table 2 Study characteristics

Study	Participants (n)	Age R in years	Age L in years	Male/ Female R	Male/ Female L
Abraham-Nordling *et al.* 2012	161	68 (59-77)	69 (62-79)	43/36	45/37
Brandstrup *et al.* 2003	141	64 (42-90)	69 (41-88)	33/36	37/35
Gao *et al.* 2012	179	72 (65-89)	73 (65-87)	54/39	49/37
Holte *et al.* 2004 (laparoscopic)	48	34 (21-65)	37.5 (23-63)	3/21	5/19
Holte *et al.* 2007 (colonic surgery)	32	73.5 (56-87)	76.5 (53-93)	6/10	9/7
Holte *et al.* 2007 (knee arthroplasty)	48	71.5 (58-80)	71.5 (55-83)	13/11	10/14
Kabon *et al.* 2005	253	53 (39-67)	52 (38-66)	60/64	65/64
Lobo *et al.* 2011	88	69.2 ± 9.0	68.8 ± 7.3	21/24	24/19

	Fluid management restrictive group during operation	Fluid management liberal group during operation	Outcome measures
	Buffered glucose 2-5% i.v. 2 mL/h/kg	Buffered glucose 2-5% i.v. 2 mL/h/kg and RL 5 mL/h/kg	**Primary**: postoperative hospital stay **Secondary**: complications within 30 days
	No replacement for third space loss, 500 mL of glucose 5% in water less oral fluid intake during fast Blood loss replaced with 6% HAES 1:1	Normal 0,9% saline; first hour 7 mL/h/kg, second and third hour 5 mL/h/kg, then 3 mL/h/kg. 500 mL normal saline 0.9% independent or oral intake during fast. Blood loss up to 500 mL: 1000-1500 mL normal saline; Blood loss > 500 mL additional HAES 6%	**Primary**: complications within 30 days **Secondary**: death and adverse effects including postoperative hypotensive episodes and renal function impairment
	RL; first hour 7 mL/h/kg, then 5 mL/h/kg Blood loss replaced with 6% HAES 1:1	RL; 12 mL/h/kg Blood loss replaced with 6% HAES 1:1	**Primary**: complications within 30 days **Secondary**: death and adverse effects
	15 mL/kg RL	40 mL/kg RL	**Primary:** Pulmonary function, exercise capacity, stress responses (aldosterone, antidiuretic hormone, angiotensin II, atrial natriuretic peptide and renin), balance function **Secondary:** pain, nausea, vomiting, hospital stay, and recovery.
	RL: first hour 7 mL/h/kg, then 5 mL/h/kg and Voluven 7 mg/kg	RL: 18 mL/h/kg and Voluven 7 mg/kg	Time to discharge, readmissions within 30 days, complications within 30 days
	RL: 10 mL/h/kg and Voluven 7 mL/kg	RL: 30 mL/h/kg and Voluven 7 mL/kg	Time to discharge, readmissions within 30 days, complications within 30 days
	RL: 8-10 mL/h/kg Blood loss 3:1 ratio with crystalloids	RL bolus 10 mL/kg before induction. Maintenance 16-18 mL/h/kg Blood loss 3:1 ratio with crystalloids	**Primary:** surgical wound infections **Secondary**: tissue oxygenation in measured in upper arm, nausea and vomiting, and post-operative pain.
	RL: 4 mL/h/kg	RL: 12 mL/h/kg	Complications within 30 days

Table 2 Continued

Study	Participants (n)	Age R in years	Age L in years	Male/ Female R	Male/ Female L
Matot *et al.* 2012	107	39.9 (18-62)	41.6 (19-72)	19/33	18/37
McArdle *et al.* 2009	22	74 (58-80)	75 (64-86)	10/1	11/2
Nisanevich *et al.* 2005	152	62.8 ± 13.4	59.4 ± 12.1	38/39	40/35
Peng *et al.* 2013	174	62 (54-79)	63 (40-87)	45/39	49/41

R = restrictive fluid management, L = liberal fluid management, RL = Ringer's lactate, HAES = Hydroxyethyl starch

	Fluid management restrictive group during operation	Fluid management liberal group during operation	Outcome measures
	RL: 4 mL/h/kg	RL: 10 mL/h/kg	**Primary**: intraoperative urine output **Secondary**: serum creatinine concentrations in the first 3 postoperative days, death and complications within 30 days
	Hartman solution: 4 ml/h/kg	Hartman solution: 12 ml/h/kg	**Primary**: complications within 30 days **Secondary**: in hospital mortality, 30-day mortality, fluid balance, length of postoperative stay, SOFA score, urinary albumin/creatinine ratio
	RL: 4 ml/h/kg	RL: 12 ml/h/kg	**Primary:** number of death and complications **Secondary**: time to initial passage of flatus and faeces, hospital stay, differences in body weight, haematocrit, creatinine, albumin serum concentration and oxygen saturation in the first 3 postoperative days, number of patients receiving transfusion of blood or blood products
	RL; first hour 7 mL/h/kg, then 5 mL/h/kg Blood loss replaced with 6% HAES 1:1	RL; 12 mL/h/kg Blood loss up to 500 mL: 1000-1500 mL normal saline; Blood loss > 500 mL additional HAES 6%	**Primary**: complications within 30 days **Secondary**: death and adverse effects

Table 3 Results of individual studies: complications within 30 days

Study	Total participants R n =	Total participants L n =	Total complications R n=(%*)	Total complications L n = (%*)	P	Bleeding R n = (%)	Bleeding L n = (%)
Abraham-Nordling *et al*. 2012	79	82	50 (39)	47 (57)	0.079	0 (0)	2 (2.4)
Brandstrup *et al*. 2003	69	72	26 (33)	83 (51)	0.013	1 (1.4)	5 (6.9)
Gao *et al*. 2012	93	86	46 (33)	84 (45)	0.079	2 (2.2)	1 (1.2)
Holte *et al*. 2004 (laparoscopic)	24	24	-	-	-	-	-
Holte *et al*. 2007 (colonic surgery)	16	16	18 (37.5)	1 (6)	0.03	1 (6.3)	0 (0)
Holte *et al*. 2007 (knee arthroplasty)	24	24	1 (4)	3 (12,5)	-	-	-
Kabon *et al*. 2005	124	129	-	-	-	-	-
Lobo *et al*. 2011	45	43	9 (20)	24 (42)	0.046	-	-
Matot *et al*. 2012	52	55	7 (13)	10 (18)	0.60	2 (3.8)	2 (3.6)
McArdle *et al*. 2009	10	11	1 (10)	14 (64)	0.024	-	-
Nisanevich *et al*. 2005	77	75	17 (17)	32 (31)	0.046	0 (0)	0 (0)
Peng *et al*. 2013	84	90	46 (35)	86 (48)	0.083	1 (1.2)	1 (1.1)

*R = restrictive fluid management group, L = liberal fluid management group, *percentage of patients with complications.*

No meta-analysis could be performed with regards to the secondary outcome measure renal function because too little data was available for valid results. Not all data could be included in the meta-analysis of total complication rate as the total amount of complications per group in some studies exceeded the total amount of patients in the group.[14, 17, 20, 22]

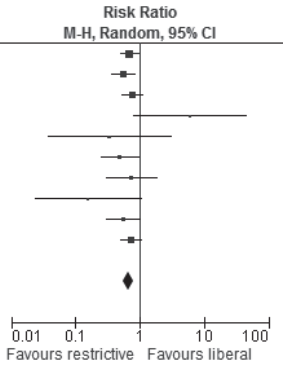
There was no difference in the amount of complications per patient in both groups (data not shown). The restrictive approach results in 35% fewer patients with a complication in our analysis. A subgroup analysis did not show any difference between studies using crystalloids only and studies using a combination of crystalloids and colloids (data not shown). A subgoup analysis for abdominal surgery only and non-abdominal surgery showed in both subgroup analysis a significant reduction in total patients with a complication which favours the restrictive approach (data not shown).

Wound infection R n = (%)	Wound infection L n = (%)	Pneumonia R n = (%)	Pneumonia L n = (%)	Sepsis R n = (%)	Sepsis L n = (%)	Cystitis R n = (%)	Cystitis L n = (%)	Peritonitis R n = (%)	Peritonitis L n = (%)
10 (12.7)	11 (13.4)	0 (0)	1 (1.2)	1 (1.3)	4 (4.9)	-	-	1 (1.3)	1 (1.2)
9 (14.5)	18 (26.4)	3 (4.3)	9 (12.5)	0 (0)	4 (5.6)	1 (1.4)	5 (6.9)	1 (1.4)	0 (0)
12 (13.8)	22 (25.6)	7 (7.5)	15 (17.4)	2 (2.2)	1 (1.2)	2 (2.2)	3 (3.5)	1 (1.1)	0 (0)
-	-	-	-	-	-	-	-	-	-
1 (6.3)	0 (0)	2 (12.5)	1 (6.3)	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-
14 (11.3)	11 (8.5)	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	0 (0)	2 (4.6)
1 (1.9)	0 (0)	-	-	-	-	-	-	-	-
0 (0)	0 (0)	0 (0)	4 (36.4)	0 (0)	1 (7.1)	-	-	-	-
7 (9.1)	11 (14.7)	3 (3.9)	5 (6.7)	0 (0)	1 (1.3)	-	-	2 (2.6)	3 (4)
9 (11.9)	20 (24.4)	7 (8.3)	15 (16.7)	2 (2.4)	1 (1.1)	2 (2.4)	3 (3.3)	1 (1.2)	1 (1.1)

1. Total of patients with a complication

Study or Subgroup	Restrictive Events	Total	Liberal Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham-Nordling 2011	31	79	47	82	23.1%	0.68 [0.49, 0.95]
Brandstrup 2003	21	69	40	72	16.3%	0.55 [0.36, 0.83]
Gao 2012	31	93	38	86	19.2%	0.75 [0.52, 1.10]
Holte 2007 (colonic)	6	16	1	16	0.8%	6.00 [0.81, 44.35]
Holte 2007 (knee)	1	24	3	24	0.7%	0.33 [0.04, 2.98]
Lobo 2011	9	41	18	40	6.8%	0.49 [0.25, 0.95]
Matot 2012	7	52	10	55	4.0%	0.74 [0.30, 1.80]
McArdle 2009	1	10	7	11	0.9%	0.16 [0.02, 1.06]
Nisanevich 2005	13	77	23	75	8.4%	0.55 [0.30, 1.00]
Peng 2013	29	84	43	90	19.9%	0.72 [0.50, 1.04]
Total (95% CI)		**545**		**551**	**100.0%**	**0.65 [0.55, 0.78]**
Total events	149		230			

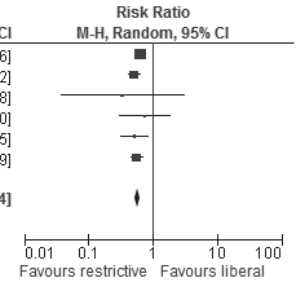
Heterogeneity: Tau² = 0.01; Chi² = 9.97, df = 9 (P = 0.35); I² = 10%
Test for overall effect: Z = 4.59 (P < 0.00001)



2. Total complication rate

Study or Subgroup	Restrictive Events	Total	Liberal Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham-Nordling 2011	50	79	81	82	39.5%	0.64 [0.54, 0.76]
Gao 2012	46	93	84	86	26.3%	0.51 [0.41, 0.62]
Holte 2007 (knee)	1	24	3	24	0.2%	0.33 [0.04, 2.98]
Matot 2012	7	52	10	55	1.4%	0.74 [0.30, 1.80]
Nisanevich 2005	17	77	32	75	4.6%	0.52 [0.32, 0.85]
Peng 2013	46	86	86	90	27.9%	0.56 [0.46, 0.69]
Total (95% CI)		**411**		**412**	**100.0%**	**0.57 [0.52, 0.64]**
Total events	167		296			

Heterogeneity: Tau² = 0.00; Chi² = 3.89, df = 5 (P = 0.57); I² = 0%
Test for overall effect: Z = 10.18 (P < 0.00001)



3. Cumulative infection rate

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham-Nordling 2011	15	79	25	82	13.6%	0.62 [0.36, 1.09]
Brandstrup 2003	14	69	36	72	15.1%	0.41 [0.24, 0.68]
Gao 2012	24	93	41	86	20.6%	0.54 [0.36, 0.82]
Holte 2007 (colonic)	3	16	1	16	1.2%	3.00 [0.35, 25.87]
Holte 2007 (knee)	1	24	0	24	0.6%	3.00 [0.13, 70.16]
Kabon 2005	14	124	11	129	8.6%	1.32 [0.63, 2.80]
Lobo 2011	7	41	9	40	6.5%	0.76 [0.31, 1.84]
Matot 2012	1	52	1	55	0.8%	1.06 [0.07, 16.48]
McArdle 2009	0	11	5	10	0.8%	0.08 [0.01, 1.34]
Nisanevich 2005	15	77	22	75	13.1%	0.66 [0.37, 1.18]
Peng 2013	21	84	40	90	19.1%	0.56 [0.36, 0.87]
Total (95% CI)		**670**		**679**	**100.0%**	**0.62 [0.48, 0.79]**
Total events	115		191			

Heterogeneity: Tau² = 0.03; Chi² = 12.43, df = 10 (P = 0.26); I² = 20%
Test for overall effect: Z = 3.90 (P < 0.0001)

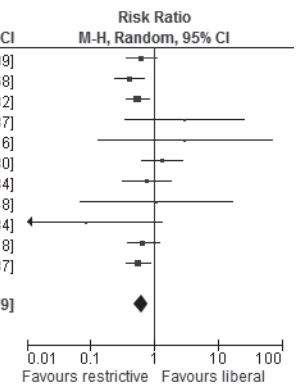
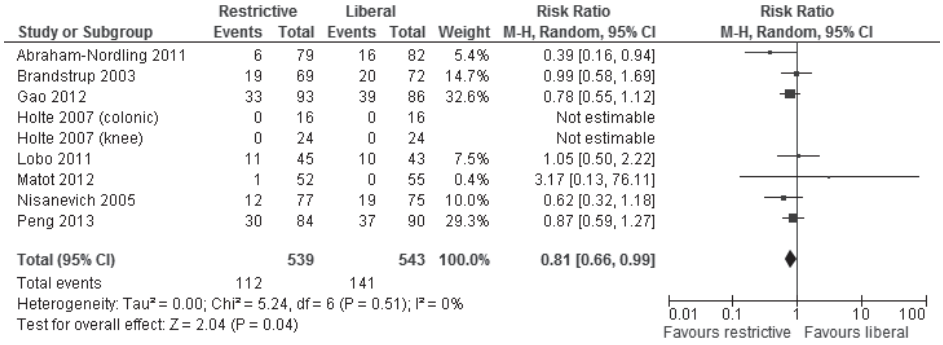


Figure 1 meta-analysis

M-H = Mantel Haenszel

4. Blood transfusion



5. Post-operative rebleeding

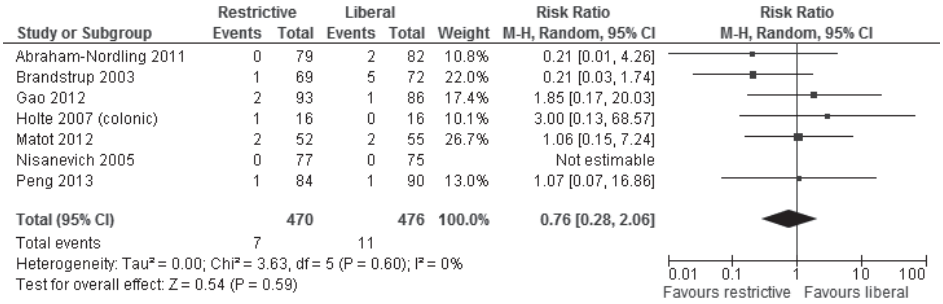


Figure 1 Continued

DISCUSSION

Fluid management during surgery is been discussed for many years yet no consensus exists on the optimal course of action. The British consensus advocates an optimal stroke volume guided fluid therapy (goal directed therapy or GDT) for orthopaedic and intra-abdominal surgery but is not directive as to what this stroke volume should be and the volume of the suggested bolus therapies are authority based.[25] No guideline is available of the American Society of Anesthesiologists and European Society of Anaesthesiology. The Enhanced Recovery After Surgery (ERAS) society advocates to avoid water and salt overloading and intraoperative GDT could be helpful to achieve this.[26]

Goal directed therapy individualises the amount of fluid given to a patient with stroke volume as the directive measurement. However, the anaesthesia itself can induce a hypotensive state, reduced urine output and reduced heart rate without the patient being hypovolemic. Therefore goal directed therapy can still lead to fluid overloading.[7, 27-30]

Our current analysis advocates for a restrictive approach. We showed that restrictive fluid management decreases 30-day complications after elective surgery. As a secondary outcome measure we detect fewer infections in the restrictive group. Additionally, transfusion need is significantly lower in restrictive groups although the blood loss did not significantly differ between both groups.

Brandstrup and co-workers report in their study higher rates of anastomotic leakage and more infections in the liberal group.[14] Both may lead to sepsis and wound healing problems. This is in line with McArdle *et al.*, Peng *et al.* and Nisanevich *et al.* who argue that tissue oedema due to the liberal fluid regimen might be responsible.[22-24] Gastrointestinal oedema results in gastrointestinal dysfunction and therefore an increased risk of anastomotic dehiscence.[31] This is supported by the results of Peng and co-workers who demonstrate the increased amount of extracellular fluids in the liberal group on the first two postoperative days. Cellular swelling impairs intracellular signalling mechanisms responsible for adequate (immune) responses.[32]

Gao *et al.*[15] shows fluid overload might promote infection due to an altered immune system. The authors demonstrate a higher CD4+/CD8+ ratio which suggest a better preserved immune response. They argue that lymphocyte signalling is impaired due to cell swelling in the liberal approach. The investigation of Holte in colonic surgery could not show more anastomotic leakage or infections.[17]

An increase of cardiovascular events could be caused by fluid overload which stresses the circulatory system. Moreover, fluid overloading contributes to pulmonary dysfunction resulting from oedema. The oedema and the potentially resulting hypoxia may give rise to respiratory failure and to pulmonary infection.[5, 33]

Although the mean amount of blood loss in the restrictive fluid management group does not differ from the mean amount of blood loss in the liberal fluid management group (mean 343 mL (0-1146 mL) versus 372 mL (0-1100 mL), respectively), the distribution of transfusion rate favours the restrictive group. This might be explained by a higher degree of haemodilution. In other words, the haemodilution seems responsible for unnecessary blood transfusion, which itself is responsible for increased mortality. The immunomodulation caused by blood transfusion may contribute to wound healing distress and infection, perhaps explaining the higher infection rate in the liberal fluid therapy group.

Finally fluid overload may interfere with coagulation. Crystalloids have shown to promote a hyper coagulant state, possibly predisposing to thromboembolic events .[5, 34, 35] The exact mechanism remains unclear but it may be due to dilution of anticoagulants

such as antithrombin III and protein C.[34] If the dilution is more pronounced the combined effects result in a coagulopathy which might promote bleeding.[36] Hydroxyethyl starches (HES) are known to interfere with platelet function, von Willebrand factor, and Factor VIII and protein C coagulation cascade promoting a hypo coagulant state in even small quantities.[37, 38] In this review the HES effects are not pronounced as only 5 used HES preparations.[17, 18] Between Holte *et al*. (colonic surgery) [17] and Holte *et al.* (knee arthroplasty) [18] the amount given per policy did not differ between the study groups. Gao *et al.*, Lobo *et al.* and Peng *et al.* gave significant different amounts of colloids to each study group. In all 5 studies there was no difference in hyper coagulant events or hypo coagulant events.

Limitations

The risk of bias is fixed at a low level because we only included randomized controlled trials. However, there are some limitations to be discussed. The heterogeneity of the included studies might be a limitation. Particularly the broad variety of participants and types of surgery can possibly influence the results. Most of the studies are single-centre which can add to the heterogeneity. In contrast, the shown advantage of restrictive fluid management in all these different patient groups induces generalizability to the world's population, improving the external validity of the results. The statistical analysis in the meta-analysis are low for heterogeneity suggesting the results are valid for the overall population.

Additionally the risk of bias in individual studies needs to be addressed. The results of quality assessment are shown in appendix 1. Overall, the quality of Brandstrup *et al.* and *Peng et al.* are best and worst appraised respectively. It has to be taken into account that not every item has the same weight. Peng *et al*., Holte *et al.* (knee and colonic) clearly describe how and when participants were selected. In all other studies the selection procedures are less clearly described. Another potential threat for overall validity is information bias. Blinded assessment of outcome measures is done in all studies. Lobo *et al*., Holte *et al.* (laparoscopic, knee and colonic), Nisanevich *et al*., and Abraham-Nordling *et al.* described blinding of surgeons for the intervention, contrary to the other studies. However, surgeons are not the primary guardians of fluid management; fluid management is the responsibility of the anaesthesiologist. Anaesthesiologists are not further involved in the study procedure and patient care thereafter limiting the risk of information bias. No study mentions blinding of patients for the allocated intervention. Because all studies are randomized controlled trials, confounding is not likely to occur. Randomization sequence was generated by a computer in all studies and allocation concealment was done by opaque, sealed envelopes. The overall bias of the individual studies is considered to be low.

We are not the first to analyse this subject. Even though other reviews exist we do contribute to the subject with our review as more recent studies have been added. The most known reviews on the subject are Corcoran *et al.* 2012, Boland *et al.* 2013, and Bundgaard-Nielsen *et al.* 2009.[39-41] Corcoran *et al.* compares goal directed, liberal and restrictive regimes in which they conclude a goal directed regime is superior to a liberal regime. They do not comment on liberal versus restrictive regime compared to each other. Since Corcoran *et al.* and Bundgaard-Nielsen *et al.* the studies of Gao *et al.* 2012, Abraham-Nordling *et al.* 2012, Matot *et al.* 2012, and Peng *et al.* 2013 have been published.[13, 15, 21, 24] Therefore we were able to perform a meta-analysis in contrast to Bundgaard-Nielsen *et al.*[41] Boland *et al.*[40] restricts itself to solely abdominal surgery. Three randomised controlled trials were included in Boland *et al.* and Corcoran *et al.* which we did not include: Vermeulen *et al.* 2009[42], Gonzalez *et al.* 2009[43] and Mackay *et al.* 2006.[44] These three trials studied the effects of postoperative fluid management therefore they do not meet our inclusion criteria. The latest review available is Eng *et al.* 2015[45] which subspecializes in colorectal surgery and pancreatic surgery. Eng *et al.* also includes Doppler guided therapy in their review. By doing so they do not research the true effect of a liberal versus a restrictive fluid management intraoperatively. The pancreatic surgery studies are all retrospective studies. One is a randomized controlled trial analysing the effects of different crystalloids used instead of the different amount administered.

CONCLUSION

Restrictive fluid management policy in comparison with a liberal fluid management policy during elective surgery generally led to fewer complications within 30 days following the procedure, a lower infection rate, and a lower need for blood transfusion. We therefore advocate a more restrictive filling policy in elective surgery.

ACKNOWLEDGEMENTS

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APPENDIX 1
QUALITY ASSESSMENT

Study	1a: title	1b: abstract	2a: rationale	2b: objectives & hypotheses
Abraham-Nordling *et al.* 2012	+	+	+	+/-
Brandstrup *et al.* 2003	+	+	+	+/-
Gao *et al.* 2012	+	+	+/-	+
Holte *et al.* 2004 (laparoscopic)	+	+	+	+
Holte *et al.* 2007 (colonic surgery)	+	+	+	+/-
Holte *et al.* 2007 (knee arthroplasty)	+	+	+	+
Kabon *et al.* 2005		+	+	+
Lobo *et al.* 2011		+/-	+	+/-
Matot *et al.* 2012	+	+	+	+/-
McArdle *et al.* 2009	+	+	+	+/-
Nisanevich *et al.* 2005		+	+	+
Peng *et al.* 2013	+		+/-	

3a: description of design	3b: changes in design after commencement	4a: eligibility criteria	4b: settings & locations	5: interventions	6a: complete definition of outcomes	6b: changes after commencement	7a: sample size determination
N/A	+	+		+/-		N/A	+
+	N/A	+		+	+	N/A	+
+	N/A	+		+		N/A	
+	N/A	+	+	+	+	N/A	+
+	N/A	+	+	+	+	N/A	+
+	+	+	+	+	+	N/A	+
	N/A	+		+	+	N/A	+
+	+	+		+	+	N/A	+
+	N/A	+	+/-	+	+	N/A	+
+	N/A	+	+/-	+	+/-	N/A	
	N/A	+		+	+	N/A	+
+	N/A	+	+	+	+/-	N/A	+/-

Study	7b: interim analyses	8a: method of random allocation sequence	8b: type of randomisation	9: allocation concealment mechanism
Abraham-Nordling *et al.* 2012		+	+	+
Brandstrup *et al.* 2003	+	+	+	+
Gao *et al.* 2012		+	+/-	+
Holte *et al.* 2004 (laparoscopic)		+	+	+
Holte *et al.* 2007 (colonic surgery)		+		+
Holte *et al.* 2007 (knee arthroplasty)		+		+
Kabon *et al.* 2005	+	+	+	+
Lobo *et al.* 2011	+/-		+	+
Matot *et al.* 2012		+	+/-	
McArdle *et al.* 2009	+/-	+		+
Nisanevich *et al.* 2005		+	+/-	+
Peng *et al.* 2013	+/-	+	+	+

10: Implementation	11a: who was blinded and how	11b: similarity of interventions	12a: statistical methods	12b: additional analyses	13a: participant flow	13b: losses with reasons	14a: dates of recruitment and follow-up
	+	N/A	+	N/A	+	+/-	+/-
+	+/-	N/A	+	N/A	+	+	+
	+/-	N/A	+/-	N/A	+	+	+
+/-	+	N/A	+	N/A	+	+	+
	+	N/A	+	N/A	+		+/-
	+	N/A	+	N/A	+	+	+/-
	+	N/A	+	N/A	+	+	
	+/-	N/A	+	N/A	+	+	+
	+/-	N/A	+	N/A	+		+
+	+/-	N/A	+	N/A	+	+	+/-
	+/-	N/A	+	N/A	+	+	
+/-		N/A	+/-	N/A	+	+	+/-

Study	14b: why trial was ended	15: baseline data	16: numbers analysed	17a: results, estimated effect size, precision	17b: effect size binary outcomes (absolute & relative)
Abraham-Nordling *et al.* 2012	N/A	+			N/A
Brandstrup *et al.* 2003	+	+	+	+/-	N/A
Gao *et al.* 2012	N/A	+		+	
Holte *et al.* 2004 (laparoscopic)	N/A	+	+	+/-	N/A
Holte *et al.* 2007 (colonic surgery)	N/A	+	+	+/-	N/A
Holte *et al.* 2007 (knee arthroplasty)	N/A	+	+	+/-	N/A
Kabon *et al.* 2005	+	+	+		N/A
Lobo *et al.* 2011	+	+	+	+	N/A
Matot *et al.* 2012	N/A	+			N/A
McArdle *et al.* 2009	+	+	+		N/A
Nisanevich *et al.* 2005	N/A	+	+	+/-	N/A
Peng *et al.* 2013	N/A	+			

	18: ancillary analyses	19: harms	20: limitations	21: generalisability	22: interpretation	23: registration	24: protocol	25: funding
	N/A	+/-			+		+	+
	N/A	+	+	+/-	+			+
	N/A	+/-	+	+/-	+	+		+
	N/A		+/-	+	+			+
	N/A	+/-	+		+			+
	N/A	+/-			+			+
	N/A	+/-	+	+/-	+		+	+
	N/A	+/-	+		+	+		
	N/A	+/-	+	+/-	+	+		
	N/A	+/-			+	+		+
	N/A	+/-	+	+/-	+			
	N/A	+/-	+	+/-				+/-

Total score

Study	Total (37 items)	Percentage of total (%)
Abraham-Nordling *et al.* 2012	18 of 31	58
Brandstrup *et al.* 2003	26 of 31	84
Gao *et al.* 2012	20 of 31	65
Holte *et al.* 2004 (laparoscopic)	24.5 of 30	82
Holte *et al.* 2007 (colonic surgery)	21 of 30	70
Holte *et al.* 2007 (knee arthroplasty)	22.5 of 31	73
Kabon *et al.* 2005	23 of 31	74
Lobo *et al.* 2011	22.5 of 32	70
Matot *et al.* 2012	19 of 30	63
McArdle *et al.* 2009	21.5 of 31	69
Nisanevich *et al.* 2005	18.5 of 30	62
Peng *et al.* 2013	16 of 31	52

APPENDIX 2
SPECIFIC DEFINITIONS OF COMPLICATIONS PER STUDY

Study	Wound infection	Pneumonia
Abraham-Nordling *et al.* 2012	n/a	n/a
Brandstrup *et al.* 2003	Surgical evacuation of pus and/or prolonged nursing care	Elevated temperature with radiographic findings
Gao *et al.* 2012	Surgical removal of pus and positive culture	1. Elevated temperature and radiographic findings **OR** 2. Elevated temperature and positive culture
Holte *et al.* 2004 (laparoscopic)	n/a	n/a
Holte *et al.* 2007 (colonic surgery)	Wound requiring drainage	Temperature > 38˚C, clinical signs, positive x-ray
Holte *et al.* 2007 (knee arthroplasty)	n/a	n/a

	Sepsis	Cystitis	Peritonitis
	n/a	n/a	n/a
	Positive blood culture with or without DIC or multi organ dysfunction.	Elevated temperature, dysuria, and positive culture	Re-operation
	Positive blood culture with or without DIC or multi organ dysfunction.	Elevated temperature, dysuria, and positive culture	Re-operation
	n/a	n/a	n/a
	n/a	n/a	n/a
	n/a	n/a	n/a

Study	Wound infection	Pneumonia
Kabon *et al.* 2005	Purulent exudate and a positive culture. 1992 revision if CDC criteria for a period of 15 days. ASEPSIS system	n/a
Lobo *et al.* 2011	CDC criteria for infections	CDC criteria for infections
Matot *et al.* 2012	Pus and positive culture	Radiographic findings (new infiltrate) plus 2 of the following: temperature > 38˚C, leucocytosis, positive sputum culture
McArdle *et al.* 2009	Infection requiring drainage	2 out 3 criteria: temperature > 38˚C, clinical signs, positive x-ray.
Nisanevich *et al.* 2005	Pus and positive culture	Radiographic findings (new infiltrate) plus 2 of the following: temperature > 38˚C, leucocytosis, positive sputum culture
Peng *et al.* 2013	Surgical removal of pus and positive culture	1. Elevated temperature and radiographic findings **OR** 2. Elevated temperature and positive culture

	Sepsis	Cystitis	Peritonitis
	n/a	n/a	n/a
	Medical guidelines of American College of Chest Physicians AND Society of Critical Care	CDC criteria for infections	CDC criteria for infections
	Bacterial infection plus 2 clinical signs (hypo/ hyperthermia, tachycardia, tachypnoea, leucocytosis or leukopenia	Positive urinary culture with clinical symptoms (dysuria, frequency, fever) or leucocytosis or urinary analysis with bacterial count > 100,000.	Requiring surgery
	Clinical signs and temperature > 38˚C or < 36˚C		n/a
	Bacterial infection plus 2 clinical signs (hypo/ hyperthermia, tachycardia, tachypnoea, leucocytosis or leukopenia	Positive urinary culture with clinical symptoms (dysuria, frequency, fever) or leucocytosis or urinary analysis with bacterial count > 100,000.	Requiring surgery
	Positive blood culture with or without DIC or multi organ dysfunction.	Elevated temperature, dysuria, and positive culture	Re-operation


3

Restrictive versus massive fluid resuscitation strategy (REFILL study): influence on blood loss and haemostatic parameters in obstetric haemorrhage, an open-label randomized controlled trial. (Study protocol)

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Trials 2018; 19:166

ABSTRACT

Background

Postpartum haemorrhage (PPH) is associated with maternal morbidity and mortality and has an increasing incidence in high resource countries, despite dissemination of guidelines, introduction of skills training and correction for risk factors. Current guidelines advise to administer almost twice the amount of blood loss as fluid resuscitation. This advice is not evidence based and could potentially harm patients.

Methods

All women attending the outpatient clinic and who are eligible will be informed about the study, oral and written informed consent will be obtained. In case of more than 500 mL blood loss and ongoing bleeding patients will be randomized to care as usual, fluid resuscitation with 1.5-2 times the amount of blood loss and fluid resuscitation with 0.75-1.0 times the blood loss, intervention group. Blood loss will be assessed by weighing all draping. A blood sample for determining haemoglobin, haematocrit, thrombocytes and conventional coagulation parameters will be taken at the start of the study, after 60 minutes and 12-18 hours after delivery. In a subgroup of women, additional thromboelastometric parameters will be obtained.

Discussion

Our hypothesis is that massive fluid administration might lead to a progression of bleeding due to secondary coagulation disorders. In non-pregnant individuals with massive blood loss, restrictive fluid management has been shown to prevent a progression to dilution coagulopathy. These data however cannot be extrapolated to women in labour.

Our objective is to compare both resuscitation protocols in women with early, mild PPH (blood loss 500-750 mL) and ongoing bleeding with as primary outcome the progression to severe PPH (blood loss > 1000 mL). This trial is registered in the Netherlands Trial Register on 11 January 2013 with registration number NTR 3789.

HIGHLIGHTS

- Current guidelines advise large amounts of clear fluid infusion on a non-evidence-based manner.
- We set up a randomised controlled trial to compare a restrictive fluid resuscitation strategy to a massive fluid resuscitation strategy in postpartum haemorrhage

BACKGROUND

Postpartum haemorrhage (PPH) is the main cause of maternal death worldwide and the main cause of severe maternal morbidity in the Netherlands and other high resource countries. It is defined by the World Health Organization as blood loss more than 500 mL in the first 24 hours after childbirth.[1] Annually in the Netherlands, more than 12,000 cases with more than 1,000 mL of blood loss are reported, and in about 750 cases more than 4 units of packed cells (PC), intensive care admittance or extensive surgical intervention is needed.[2] In total, 33.7% of all women in labour will have more than 500 mL blood loss, 5-13%[3, 4] of whom will experience blood loss of more than 1,000 mL and an additional 24.3% will have blood loss of 500 to 1,000 mL.[3]

Recent publications have shown an increasing trend in PPH in different high resource countries over the past years.[5] This increase is not directly linked to an increase in women with risk factors for PPH. Two retrospective studies performed in Australia and Canada concluded that although the frequency of risk and protective factors for PPH changed during the study period, correction for these factors did not alter the increasing trends in PPH.[6, 7]

Also in the Netherlands the increasing trend in PPH is observed despite the introduction of national measures to improve care for this population.[4, 8]

Despite the implementation of guidelines, regular training and obligatory courses, the incidence of PPH is still rising, which is all the more reason to evaluate currently advised protocols for managing PPH. Conclusive evidence for optimal haemostatic resuscitation in PPH is lacking.[9] The MOET (Managing Obstetric Emergencies and Trauma course) and RCOG (Royal College of Obstetricians and Gynaecologists) instructions advice generous volume resuscitation to restore the blood volume and oxygen carrying capacity: about two times the lost volume and up to 3.5 litres of fast fluid infusion in unstable bleeding patients.[10, 11] The Dutch guidelines advise to start volume resuscitation when there is profuse blood loss, the specific amount is not quantified. This guideline is based on the

same (animal) studies mentioned later in this protocol.[12] Volume resuscitation can be done with crystalloids, colloids or red blood cells (RBC) in different volume strategies which all have advantages and disadvantages (see discussion for a more detailed outline). Our hypothesis is that massive fluid administration might lead to a progression of bleeding due to secondary coagulation disorders in women with PPH.

METHODS AND DESIGN

Aims

The aim of the REFILL study is to determine whether in women with early, mild PPH (blood loss 500-750 mL) and ongoing blood loss, restrictive fluid resuscitation strategy reduces the progression to severe PPH (defined as blood loss > 1000 mL) compared to care as usual. We hypothesise that restrictive fluid resuscitation will lead to a decrease in progression to severe PPH and therefore a decrease in its adverse outcomes.

Participant's criteria and recruitment

In this multicentre study women with 500 – 750 mL blood loss postpartum and ongoing bleeding will be eligible for the study. The study will be performed in three Dutch hospitals, two university hospital (Maastricht University Medical Centre, Radboud University Medical Centre) and one regional teaching hospital (Zuyderland Medical Centre). The Maastricht Medical Centre is the coordinating centre.

All women attending the outpatient clinic or admitted to the ward and not in active labour who meet the inclusion criteria (see further) will be informed about the study by the treating physician or research nurse. Oral and written informed consent is obtained. When women present at the labour ward, they will be asked to orally confirm whether they still want to participate in the study. (See figure 1)

Inclusion criteria are:

- Pregnant and labour starting after 24+0 weeks
- Age ≥ 18 years
- Informed consent
- Mentally competent, understanding Dutch language

Exclusion criteria are:

- Prophylactic or therapeutic anticoagulant therapy (carbasalate calcium within the last 10 days or low molecular weight heparins within last 48 hours)
- Known congenital coagulation disorders

- Pre-eclampsia (higher risk of low plasma volume, higher risk of volume overload)
- Antenatal diagnosed placenta accrete/increta/percreta
- Contraindication for massive fluid therapy (e.g., cardiac causes, systemic causes (Marfan), renal causes, pulmonary failure)

Randomisation, procedures and collection of data

In women with more than 500 mL blood loss and ongoing blood loss, randomisation takes place. Treatment allocation is blinded by use of opaque and sealed envelopes. The randomisation is stratified per centre, in blocks of 4 and concealed in allocation of 1:1. The envelopes will be distributed per centre by Maastricht University Medical Centre. The required randomisation envelopes will be quickly and easily accessible at the labour ward. Participants will be randomised to either intervention group (receiving fluids at 0.75 – 1.0 times the blood loss) or care as usual: control group (receiving fluids at 1.5 – 2.0x blood loss).

In women participating in the study, blood loss will be measured by weighing the absorption towels after child birth, excluding the first one directly after giving birth which includes amniotic fluid. In current care, generous volume resuscitation is standard; this consists of about two times the lost volume and two litres fast infusion in unstable bleeding patients. Volume resuscitation will be done with a fast infusion of crystalloids or Ringer's lactate primarily. In all women the first 2000 mL will consist of a fast infusion of NaCl (0.9%) and/or Ringer's lactate.

At the stage of 500 - 750 mL blood loss the study protocol starts (T1). Intravenous access will be established and a blood sample taken for testing haemoglobin (Hb), haematocrit (Ht), platelet count, aPTT, PT and fibrinogen. Women delivering in the Maastricht University Medical Centre ROTEM® analysis will be included (FIBTEM, APTEM, INTEM, EXTEM). Hemodynamic parameters include blood pressure and continuous pulse oximetry.

Additionally clinical parameters will guide management and will serve as a safety check. We aim to maintain the systolic blood pressure > 90 mmHg and the diastolic blood pressure > 50 mmHg, and/or a drop of less than 20 mmHg. The maternal heart rate should be less than 125 beats per minute.[13] In case of crossing these cut off values, in both groups an additional volume of 500 mL will be administered in 15 minutes.

45-60 minutes after the initial start of infusion at T2 two situations can occur:

1. The patient is stable, defined as normal on-going blood loss (< 1 full sanitary pad/ hour) with stable blood pressure and pulse. At this point we will take an extra blood sample for of Hb, Ht, platelets, aPTT, PT and fibrinogen.

2. The patient is still bleeding, defined as > 100 mL/hour. In case of more than 1 full sanitary pad/hour the blood loss will be weighed again. Laboratory tests for Hb, Ht and coagulation status is part of regular care.

At T3, 12-18 hours postpartum, the last blood sample will be taken for Hb and Ht. This is part of regular care in women with blood loss > 500 mL.

In case of > 1500 mL blood loss the study protocol will be terminated and patients will be treated according to local massive haemorrhage protocol. Blood samples will still be drawn and the patient will be analysed on an intention-to-treat basis.

Except for the fluid resuscitation, treatment of the underlying cause of the PPH will be according to the local and national protocol in both groups (NVOG [Nederlandse Vereniging voor Obstetrie en Gynaecologie] guideline), which will be noted in the clinical chart and registered in the trial data. We expect this to be similar in both groups. The NVOG guideline advises basal preventive measures to identify women at high risk which consist of: an active third stage of labour consisting of pre-labour use of an IV access and recently known and matched blood type, weighing the amount of blood loss when the blood loss seems profuse and a preventive administration of 5 IE of oxytocin intravenously after childbirth and before placental birth. In women at high risk of PPH an additional 10 IE oxytocin is administered in a course of 4 hours postpartum. The guideline does not recommend tranexamine acid in preventive setting yet. If oxytocin is not or only partially effective Sulproston (500 micrograms in 30 minutes followed by 60-120 micrograms per hour) or methylergometrine (0.2 mg intravenously or intramuscular) is recommended. If blood loss is more than 1000 mL or when more than 2000 mL crystalloids are given, the guideline advises to perform blood tests (APTT, PT, thrombocytes, fibrinogen or thromboelastometry if available) and correct deficiencies accordingly. In expectation of the laboratory results fibrinogen or tranexamine acid can be administered. This recommendation dates from after the start of the study.

Other study parameters regarding the obstetric history and the current pregnancy will be collected from the patient's chart.

All data is collected and stored anonymously in Maastricht Medical Centre in a restricted access file. A trial number is assigned to each patient which will be used in the dataset as to ensure anonymous data collection, these trial numbers are stored securely and locked from the dataset. Data will be imputed as soon as possible after study participation. Dataset will be saved separately marked by date of saving. Data will be stored for 15 years. PS, NL, HS, LS will have access to final data set.

Outcome measures

Primary objective

The primary objective is to establish whether in women with early, mild PPH (blood loss 500 – 750 mL) a fluid resuscitation strategy with fluids 0.75 – 1.0 times the blood loss reduces the progression to severe PPH (defined as blood loss > 1000 mL) compared to fluid resuscitation with fluids 1.5 - 2.0 times the blood loss.

Secondary objective

Secondary outcomes are: difference in Hb (mmol/l) 12-18 hours postpartum (including differences in Hb < 5,0 mmol/l), differences in transfusion requirements (defined as the number of packed red blood cells, fresh frozen plasma, thrombocytes and fibrinogen needed), differences in the amount of coagulopathies defined as individually abnormal laboratory results according to current treatment protocols (meaning platelets < 50x10*9, fibrinogen < 1g/L and APTT and PT > 1,5x mean control).

Severe adverse outcomes will be registered. We define serious adverse outcomes as intensive care admittance, the need of 4 or more packed cells, embolization and hysterectomy [2]

Statistical analysis

The between-group difference in the proportion of women progressing from early mild PPH to severe PPH and its confidence interval will be calculated. Descriptive analysis will be carried out for baseline characteristics, i.e. maternal age, ethnical background, parity (nulliparous / multiparous), gestational age, obstetric history, length, weight, use of oxytocin, mode of delivery (vaginal delivery/instrumental delivery/caesarean section), delivery of placenta (spontaneously/manual), life birth and birth weight. All different treatments to resolve the underlying cause of PPH given to the patient will be registered. Severity parameters will be described, i.e. intensive care admittance, the need of 4 or more packed cells, embolization or hysterectomy.

Total blood loss, transfusion need and laboratory results will be compared by use of either the Student's T-test for continuous outcomes or the Chi-square test for dichotomous outcomes. In case of non-normality, mathematical transformation will be carried out of continuous outcomes. In case of large differences in important prognostic variables at baseline (which are unanticipated in view of the randomisation), multivariable logistic or linear regression analysis will be employed controlling for these variables. Analysis will be by intention to treat. Missing data will not be imputed by use of multiple imputation. All data will be analysed in IBM SPSS 24.0 software.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation			Close-out	
TIMEPOINT	*Visit outpatient clinic ($-t_1$)*	*500cc blood loss*	*t_1'*	*t_2''*	*t_3'''*	*After discharge patient*	
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Restrictive fluid resuscitation			X	X	X		
Standard fluid resuscitation			X	X	X		
ASSESSMENTS:							
Baseline variables*						X	
Outcome variables**						X	

Figure 1 SPIRIT

SPIRIT flow diagram.
**t1 at 500–750 cm3, resuscitation within randomized protocol starts, blood withdrawal.*
***t2, 45–60 min after t1, second blood withdrawal. ***t3 12–18 h after t1, third blood withdrawal.*
***** i.e. maternal age, ethnic background, parity (nulliparous or multiparous), gestational age, obstetric history, length, weight, use of oxytocin, mode of delivery (vaginal delivery, instrumental delivery, or Caesarean section), delivery of placenta (spontaneous or manual), life birth, and birth weight.*
****** All different treatments to resolve the underlying cause of PPH given to the patient will be registered, intensive care admittance, the need of four or more units of packed cells, embolization, and hysterectomy, laboratory results at t1, t2, and t3*

Sample size calculation

In the current care about 30% off all women will proceed from 500 to 1000 mL of blood loss. With a reduction from 30 to 15% (beta 0.80, alpha 0.05) 2x 118 (236) women will have to be included. We aim to include 250 women in order to compensate for loss to follow up and/or incomplete data.

Safety concerns

A Data Safety Monitoring Board is established to perform ongoing safety surveillance and interim analyses on the safety data. The board will be informed in any case of a severe adverse event. The DSMB is composed of 3 independent physicians: drs. N.M.A.A.

Engels (anaesthetist), dr. J.M. Middeldorp (gynaecologist from a hospital not involved in the trial), dr. A Kessels (epidemiologist). Drs. N.M.A.A. Engels is chairman of the DSMB. Further details about the DSMB in a separate charter available upon request.

The DSMB will meet by teleconference after the first 2x25 patients and every 50 thereafter per group and do an interim analysis on the primary objective and the composite measure severe outcome (maternal death, use of > 4 packed cells (PC), intensive care admittance, embolization or operative intervention.) The formulas proposed by Prochan, Lan and Wittes (2006) will be used for the interim analysis.

In the analysis done by the DSMB a correction will be done for possible confounders for the primary outcome, such as risk factors for PPH and difference in combined severe outcome. Should there be a statistically significant difference in severe adverse events between the intervention and the control group which cannot be accounted to other factors such as selection bias in small groups, the DSMB shall decide whether the study should be continued. The study could be terminated prematurely on advice of the DSMB if one of the treatment protocols shows less progression tot severe blood loss and less maternal morbidity; in this case it is ethically not justified to continue the study. All communications by the DSMB are reported back via email to HS and PS. The final decision to terminate the trial after advice of the DSMB is with HS.

The trial is overseen by PS and HS. They are responsible for all communications with participating hospitals and local research nurses as responsible for communication with the DSMB, ethical committee and trial registration bureau. Insurance policies are available to patients in case of adverse outcomes with lasting effects due to study intervention.

DISCUSSION

PPH is increasing in incidence in industrialised countries and is without evidence-based managing protocol regarding fluid resuscitation. Volume resuscitation can be done with crystalloids, colloids or red blood cells (RBC), which all have advantages and disadvantages. Resuscitation with crystalloid fluids means large amounts are needed which may induce acidosis and coagulopathy, formation of interstitial oedema and impairment of the microcirculation.[14] Colloid fluids, in particular synthetic colloids like hydroxyethyl starch solutions (HES), may impair clot formation and therefore increase blood loss.[15, 16] Furthermore, even new generation medium molecular weight HES disturb fibrin polymerization in patients undergoing spine surgery[17] and the presence of HES or gelatine solutions in patients with fibrinolysis leads to faster clot disintegration.[18] Once

30-40% of the circulating blood volume is lost, RBC replacement will be required. RBC cannot be used for massive fluid therapy and one must be careful to use uncross-matched blood, especially in young fertile women, because of the possibility of irregular anti-body formations and its effect on future pregnancies.

Restrictive or permissive resuscitation has recently been advocated as an alternative to the current standard care. In animal studies, military settings and in non-pregnant trauma patients controlled hypotensive resuscitation has been investigated, these studies have shown that there might be an advantage for a restrictive fluid resuscitation strategy. However, there are few well-performed randomised controlled trials. This might be due to ethical concerns in life threatening conditions, but is nonetheless important to improve survival and morbidity relying on evidence-based medicine. Until recently high-volume fluid resuscitation strategies have been used to reverse haemorrhagic shock by replacing blood loss with intravenous fluid or transfusions. This strategy has been the gold standard even though it has not been tested in prospective randomized clinical trials and has considerable limitations and risks. Increasing evidence has demonstrated that aggressive crystalloid-based resuscitation strategies are associated with cardiac and pulmonary complications, gastro-intestinal dysmotility, coagulation disorders and immunological and inflammatory mediator dysfunction. Aggressive fluid administration increases arterial and venous pressures, but aggravates dilution of clotting factors and blood viscosity which results in increased haemorrhage volume, decreased oxygen delivery and decreased survival rates.[19] Continued fluid administration and positive fluid balances have not been shown to improve renal outcomes and may worsen overall prognosis in acute kidney failure.[20] Also, maintaining a high or 'normal' blood pressure in patients with uncontrolled haemorrhagic shock can result in the "lethal triad" of hypothermia, acidaemia and coagulopathy.[21]

Theoretical concerns regarding the safety of restrictive resuscitation are based on the possible harmful effects of decreased oxygen delivery to the various tissues of the body due to shock. Maintaining a blood pressure that is too low could potentially result in inadequate perfusion and subsequent organ failure. Intraoperative restrictive resuscitation has been successfully used in several animal models.[22] The results of Lu *et al.* showed that aggressive fluid resuscitation to restore near normal MAP of 80 mmHg during uncontrolled haemorrhage induced massive blood loss and excessive haemodilution. Controlled fluid resuscitation to maintain MAP of 40 mmHg in the presurgical treatment of severe and uncontrolled haemorrhagic shock decreased further blood loss, avoided excessive haemodilution and coagulopathy, improved the early survival rate, and reduced the apoptosis of the visceral organs.[23]

Two randomised controlled trials investigated restrictive resuscitation protocols in trauma patients. The preliminary results on 90 patients in a randomised controlled trial conducted by Morrison *et al.* showed fewer early postoperative deaths and significantly fewer blood product transfusions in the study group, without differences in the incidence or severity of coagulopathy, thrombocytopenia or anaemia. In this study the difference in mean arterial pressure (MAP) between both study groups was not statistically significant and the actual MAPs for the two groups were much more similar than might be expected based on the target goals for resuscitation.[24] The final results of this trial including the targeted 271 patients have not been published yet. Dutton *et al.* found no significant difference in mortality between the study groups in which maintaining a systolic blood pressure > 100 mmHg was compared to targeting a systolic blood pressure of 70 mmHg.[25] One of the limitations of this study is that there was no power analysis performed before initiating the study and the sample size (n = 110) Also, as in the previous study, the proposed target blood pressure in the study group was not achieved.

A retrospective analysis by Duke *et al.* in trauma patients showed an overall lower mortality rate, lower intra-operative mortality and a shorter hospital stay in the restrictive resuscitation group. Despite the fact that the groups were well-matched, the retrospective character of the study is a limitation and bias cannot be ruled out.[26]

A prospective randomised pilot trial comparing controlled resuscitation versus standard resuscitation in hypotensive trauma patients demonstrated that controlled resuscitation strategy can be successfully and safely implemented in a civilian environment. The results showed a reduction of early crystalloid resuscitation volume, but also an increase in early blood product transfusion.[27]

The studies mentioned above all encountered difficulties in performing the study strictly according to study protocol. This may be explained due to these studies were performed in an acute setting and the impossibility to blind the treating clinicians who might be less familiar with restrictive resuscitation.

Concluding, there is little and contradictive evidence for either aggressive or restrictive fluid resuscitation and it is very difficult to perform good clinical trials. This is reflected in the latest guidelines. The European Society of Anaesthesiology (ESA) guideline on management of severe perioperative bleeding recommends avoidance of hypervolemia. Permissive hypotension is not mentioned, but implementation of delayed or low-volume resuscitation protocols is not yet recommended.[28] On the other hand, the updated European guideline on management of bleeding and

coagulopathy following major trauma recommend a target systolic blood pressure of 80 to 90 mmHg until major bleeding has been stopped in the initial phase following trauma without brain injury.[29]

All these results, mainly in trauma patients, cannot be extrapolated to pregnant women during labour in view of the physiological hemodynamic and haemostatic changes that occur in pregnancy.[30, 31] Plasma volume increases up to 40% during pregnancy whereas red blood cell count only increases by 30%, cardiac output is increased and systolic and diastolic blood pressure drop slightly in the second trimester and elevate towards term pregnancy. At the end of normal pregnancy, changes in the coagulation and fibrinolytic system result in an apparent hypercoagulable state,[32-34] to minimise blood loss at delivery. In patients with PPH, this equilibrium will be altered and may lead to profound and rapid changes in haemostasis. In some cases, the disruption of the coagulation precedes delivery and may contribute significantly to developing PPH.[35] Timely recognition and prompt intervention are crucial for successful management of PPH.[36] In non-pregnant individuals with massive blood loss, restrictive fluid management has been shown to prevent a progression to dilution coagulopathy.[15-18]

In conducting this study, we hope to find the best managing option for treating PPH with a decrease in adverse outcomes due to reducing the severity of PPH.

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4

Restrictive versus liberal fluid resuscitation strategy, influence on blood loss and haemostatic parameters in mild obstetric haemorrhage: an open-label randomized controlled trial. (REFILL study)

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ABSTRACT

Background

Evidence for optimal haemostatic resuscitation in postpartum haemorrhage (PPH) is lacking. Liberal fluid administration may result in acidosis, hypothermia and coagulopathy.

Objective

We hypothesize that in early PPH a restrictive fluid administration results in less progression to moderate PPH.

Study Design

In four Dutch hospitals we recruited women of 18 years and over, and more than 24 weeks pregnant. Exclusion criteria were: anticoagulant therapy, known coagulation disorders, pre-eclampsia, antenatal diagnosis of abnormally adhesive placenta, and a contraindication for liberal fluid therapy. We blindly randomized participants at 500 mL and ongoing blood loss in the third stage of labour between restrictive fluid administration (clear fluids 0.75-1.0 times the volume of blood lost) and liberal fluid administration (clear fluids 1.5-2.0 times the volume of blood lost). The primary outcome was progression to more than 1000 mL blood loss. Analyses were according to the intention-to-treat principle. Trial registration NTR3789.

Results

From August 2014 till September 2019, 5190 women were informed of whom 1622 agreed to participate. A total of 252 women were randomized of which 130 were assigned to the restrictive group and 122 to the liberal group. In the restrictive management group 51 of the 130 patients (39.2%) progressed to more than 1000 mL blood loss versus 61 of the 119 patients (51.3%) in the liberal management group (difference, -12.0% [95%-CI -24.3% to 0.3%], p = 0.057). There was no difference in the need for blood transfusion, coagulation parameters, or in adverse events between the groups.

Conclusions

Although a restrictive fluid resuscitation in women with mild PPH could not been proven to be superior, it does not increase the need for blood transfusion, alter coagulation parameters, or cause a rise in adverse events. It can be considered as an alternative treatment option to liberal fluid resuscitation.

INTRODUCTION

Postpartum haemorrhage (PPH) is one of the most common reasons for peripartum intensive care unit (ICU) admittance and the main cause of maternal death worldwide. In high resource countries an increase in incidence of PPH is observed.[1-4] In the Netherlands the incidence of PPH rose from 4.1% in 2000 to 6.4% in 2013.[5]

Evidence for optimal haemostatic resuscitation in PPH is currently lacking.[6] The Managing Obstetric Emergencies and Trauma course (MOET) and the Royal College of Obstetricians and Gynecologists (RCOG) instructions advise generous volume resuscitation to restore blood volume and oxygen carrying capacity: about twice the lost volume and up to 3.5 L of fast fluid infusion in patients with more than 1000 mL blood loss or clinical shock.[7, 8] Dutch guidelines recommend to commence volume resuscitation at profuse blood loss, not disclosing a minimum amount of blood loss. This guideline states that there is currently no evidence to administer more fluids than lost.[9]

Resuscitation with crystalloids and colloids have their own (dis)advantages and risks. Transfusing large amounts of crystalloids before commencing with blood products may result in acidosis, hypothermia and coagulopathy; the lethal triad.[10] Additionally, the hydroxyethyl starch solutions may impair clot function when used excessively.[11]

Restrictive or permissive hypotension has been advocated as an alternative for liberal fluid resuscitation in other areas than obstetric care, although the amount of randomized controlled trials is limited. A restrictive fluid administration policy in other fields has shown to decrease further blood loss and the amount of blood transfused.[12-17] Physiological hemodynamic and haemostatic changes in pregnancy make that these result cannot be readily adopted in the postpartum haemorrhage care. During pregnancy plasma volume and red blood cell count increases 40% and 30% respectively. Cardiac output is increased and the blood pressure decreased in the second trimester and increased again at term.[18, 19] There is a hypercoagulable state during pregnancy which is most pronounced in the third trimester.[20, 21] Two recent retrospective obstetric studies, showed that larger quantities of crystalloid volume administrated in the care of women with severe PPH was associated with a more severe deterioration of coagulation parameters. Fluid resuscitation with more than 4 L of crystalloid infusion was associated with more subsequent bleeding and adverse maternal outcomes (intensive care admittance, embolization, hysterectomy).[22, 23] To date there are no publications on randomized trials on optimal fluid resuscitation in women with PPH.

The aim of this randomized controlled trial was to determine if a restrictive fluid administration policy in early and mild PPH (500 mL blood loss) leads to a decrease in progression to more than 1000 mL blood loss compared to care as usual. We included both women with a caesarean and vaginal delivery. Although the risk of PPH is higher in women with a caesarean delivery, the question on optimal fluid administration is valid for both groups.[24, 25] We hypothesized a decrease in progression and therefore a decrease in adverse outcomes.

MATERIALS AND METHODS

Study design

REFILL was a randomized controlled multicentre trial performed from August 2014 until September 2019 in four hospitals in the Netherlands. This study was approved by the Medical Ethics Committee Maastricht University Hospital (NL4294206813). This trial is registered in the Netherlands Trial Register NTR3789 or NL3623 (date of registration, 11 January 2013). The study protocol was published in 2018.[12] The study protocol is available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5838856/

Participants

Participants were recruited in four Dutch hospitals, two university hospitals (Maastricht University Medical Center, Radboud University Medical Center) and 2 regional teaching hospitals (Zuyderland Medical Center and Jeroen Bosch Hospital). Maastricht University Medical Center (MUMC) was coordinating centre. All four centres have in-house midwives and medical residents (junior and senior), and a supervising gynaecologist on call.

All women attending the outpatient clinic or the labour ward, and not in active labour, were considered for eligibility. These women were informed about the study if they met the inclusion criteria. The inclusion criteria were: age 18 years and over, understanding of the Dutch language, pregnant and labour starting after 24+0 weeks, and mentally competent. Both vaginal and caesarean deliveries were included. Exclusion criteria were: prophylactic or therapeutic anticoagulant therapy (carbasalate calcium within the previous 10 days or low molecular weight heparins within previous 48 h), known congenital coagulation disorders, pre-eclampsia, antenatal diagnosis of placenta accreta spectrum (due to likelihood of reaching primary outcome regardless of management), and contraindication for liberal fluid therapy (e.g., cardiac causes, systemic causes (Marfan), renal causes, pulmonary failure). We obtained written informed consent from all participants.

Randomization and masking

Women who gave oral and written consent for the study were randomized if they reached 500 mL and ongoing blood loss postpartum. Enrolment was performed by the treating team of caregivers at that time through sealed opaque envelopes.

Treatment allocation was blinded by the use of sealed opaque envelopes including a trial number. Randomization was stratified per centre, in blocks of four in an allocation of 1:1. Sequence was generated online (https://www.randomizer.org/) and the sealed opaque envelopes were created by an independent research nurse or medical student not involved in the randomization of the patient. Local investigators were blinded to block size and allocation. Randomization envelopes were distributed per centre by Maastricht University Medical Center.

Procedures

The randomization envelopes were quickly and readily available on the labour ward or operating theatre. In case of 500 mL and ongoing blood loss at the third stage of labour an envelope was opened by the treating physician. The patient was either randomized to the restrictive fluid administration (intervention) group or to the liberal fluid administration (control) group. In the intervention group patients received fluids at 0.75-1.0 times the volume of blood loss. In the control group patients received 1.5-2.0 times the volume of blood loss. Blood loss was measured by weighing the absorption towels after childbirth. The first towel was disposed directly after childbirth and not measured as this also includes amniotic fluids. Blood loss during caesarean section was measured through suction and weighing operative gauzes after childbirth. The first 2000 mL of volume replacement consisted of NaCl 0.9% or Ringer's lactate, or a combination of both on room temperature.

At 500 mL and ongoing blood loss allocation took place. Directly after randomization, moment T1 was initiated. If intravenous access was not yet present, intravenous access was established and blood samples for T1 were drawn. At T1 haemoglobin concentration, haematocrit, platelet count, activated partial thromboplastin time, prothrombin time, and fibrinogen concentrations were measured.

Hemodynamic parameters such as blood pressure and oxygen saturation were observed according to local protocol. Additional safety measures were taken in case of systolic blood pressure < 90 mmHg, diastolic blood pressure < 50 mmHg, a decrease of more than 20 mmHg in blood pressure, or a maternal heart rate of 125 beats per minute or more. In this case 500 mL additional volume was administered in 15 minutes in either group.

The second evaluation, T2, was 45-60 minutes after T1. At T2 a second set of blood samples as stated above were drawn. At T3, 12-18 hours post-partum a third set of blood sample was drawn for haemoglobin and haematocrit analysis only, if patients were still admitted to hospital.

If the patient reached 1500 mL blood loss the study protocol was exited and the patient was treated according to local massive obstetric haemorrhage protocol which also includes the blood transfusion policy. Blood samples as stated above were still drawn and patient data was analysed on an intention-to-treat basis.

Third stage of labour was actively managed in all participants according to national protocol with the administration of 5 IE of oxytocin directly after childbirth and 10 IE oxytocin infused in 4 hours thereafter. Patients were kept warm. The underlying cause of the PPH was treated according to local and national guidelines (Dutch Society of Gynaecology and Obstetrics, NVOG).[9]

All study parameters were collected from the patient chart and study files. The data were collected and stored anonymously in Maastricht University Medical Center in a restricted access file. A trial number was assigned to each patient at time of randomization.

Outcomes

The primary outcome was the frequency of progression to major PPH (defined as blood loss > 1000 mL). Secondary outcomes were the differences in haemoglobin concentration (mmol L^{-1}) 12-18 hours postpartum (including haemoglobin < 5 mmol L^{-1}), differences in transfusion requirements (number of units of packed red blood cells, fresh frozen plasma, thrombocytes, and fibrinogen concentrate needed), differences in coagulopathies (platelets < $50.10^{\wedge 9}$ L^{-1}, fibrinogen concentration < 1g L^{-1} and activated partial thromboplastin time (APTT) and prothrombin time (PT) > 1.5x mean control).

Severe adverse outcomes (SAE), defined as intensive care admittance, the need of four or more units of packed cells, embolization, and hysterectomy, were registered and analysed by a data safety monitoring board (DSMB).

Statistical analysis

Sample size was calculated with the assumption that, with standard care, around 30% of the women with 500 mL blood loss would progress to more than 1000 mL blood loss.[12] We calculated that, in order to be able to detect a 50% relative reduction, with a power of 0.80 and an alpha of 0.05, 118 patients would be needed in each study arm. To be able to compensate for incomplete data we aimed for 250 inclusions.

Comparative analysis was performed with either a Student's *t* test in case of continuous data or the chi-square test in case of dichotomous outcomes. Multivariable linear regression analysis was employed to check whether results were sensitive to controlling for baseline characteristics, including centre of inclusion. Analyses were done according to the intention-to-treat principle. Missing data were scarce and not imputed. Analyses were performed using IBM SPSS 24.0 and SAS version 9.4.

A data safety monitoring board was established. The DSMB was notified at each SAE, after the first 2x 25 inclusions, and every 2x 50 inclusions thereafter for which they performed an interim analysis on the primary outcome and SAEs. Throughout the study there was no need to stop the trial prematurely.

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between August 2014 and September 2019 5190 patients were assessed for eligibility of which 1622 patients gave informed consent to participate if they reached 500 mL blood loss postpartum. A total of 252 patients were randomized, 130 were assigned a restrictive fluid administration strategy, and 122 a liberal fluid administration strategy (figure 1). Maastricht University Medical Center recruited 74 participants, Radboud University Medical Center 37 participants, Zuyderland Medical Center 134 participants, and Jeroen Bosch Hospital recruited 7 patients.

Table 1 shows baseline characteristics, which were similar for the two groups. For all patients risk factors for PPH were evaluated (see supplement 1 for the risk factors collected). In two women no risk factors for PPH were present, the mean number of risk factors was 3 in both groups. In the liberal resuscitation strategy arm three patients discontinued treatment as they were diagnosed with pre-eclampsia. In the restrictive strategy arm no patient discontinued treatment. 130 patients in the restrictive fluid administration strategy, and 119 patients in the liberal fluid administration strategy were analysed as intention-to-treat. The total mean crystalloid fluid administration after randomization in the restrictive arm was 1078 mL (SD1029 mL, median 800 (0 - 5200 mL)) and 1534 mL (SD 957 mL, median 1350 mL (0 - 4100 mL)) in the liberal arm (p = 0.000). All patients received crystalloids. Additional colloids were administered in 10/130 (7.7%, 48 mL SD 220) women in the restrictive arm versus 8/119 (6.7%, 47 mL SD 171) in the liberal arm (p = 0.957).

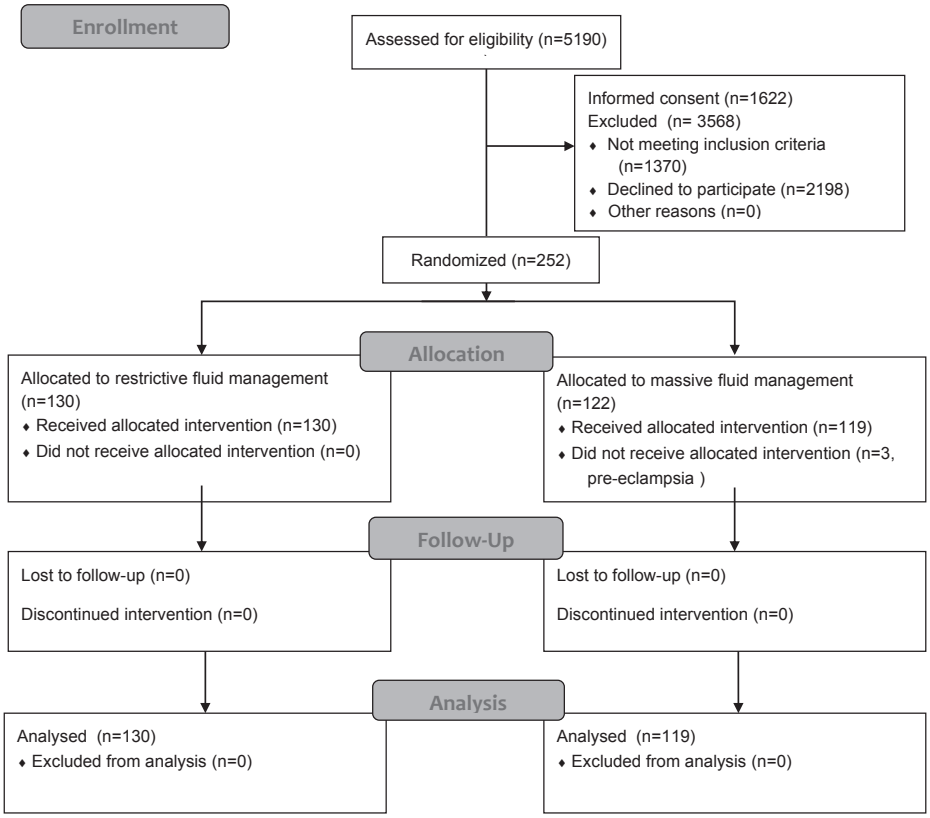

Figure 1 Flow diagram.

Table 1 Baseline characteristics

	Restrictive (n = 130)	Liberal (n = 119)
Age (years)	31.9 (±3.5; 22-41)	31.6 (±4.5; 19-45)
BMI kg m^{-2}	25.6 (±5.5; 17-45)	26·2 (±5.5; 17-47)
Gestational age (weeks)	39.2 (±1·8; 30.4-42.3)	39.3 (±1.6; 31.5-41·6)
Gravidity	2 (1-7)	2 (1-7)
Parity	0 (0-4)	1 (0-3)
Gestational age (days)	276 (±12.7; 214-297)	276 (±10.9; 222-293)
Risk factors HPP (amount)	3 (0-10)	3 (1-8)
History of:		
Manual removal of placenta	10 (7.7)	4 (3.3)
Postpartum haemorrhage	19 (14.6)	15 (12.3)
Blood transfusion with postpartum haemorrhage	8 (6.2)	6 (4.9)

Table 1 Continued

	Restrictive (n = 130)	Liberal (n = 119)
Onset of labour		
Spontaneously	31 (23.8)	31 (25.4)
Induction	83 (63.8)	77 (63.6)
Caesarean, planned	16 (12.3)	13 (10.7)
Pain relief		
Opioids	24 (18.5)	17 (13.9)
Epidural	57 (43.8)	63 (51.6)
No pain relief	50 (38.5)	28 (23.5)
Outcome		
Delivery		
Spontaneously	89 (68.5)	84 (68.9)
Ventouse	13 (10)	10 (8.2)
Caesarean	28 (21.6)	27 (22.1)
Caesarean, unplanned	12 (9.2)	19 (12.6)
Augmentation	80 (61.5)	84 (68.9)
Episiotomy	46 (35.4)	51 (41.8)
Vaginal rupture	52 (40)	48 (39.3)
Weight at birth (gram)	3497 (±631; 1470-5130)	3552 (±569; 1922-4740)
Macrosomia (> 4 kg)	28 (21.5)	26 (21.3)
T1 laboratory parameters		
Hb (g L^{-1})	112.8 (±16.1; 61.2-143.4)	112.8 (±12.9; 67.7-138.6)
Ht (%)	0.33 (±0.05; 0.18-0.43)	0.33 (±0.04; 0.21-0.42)
Thrombocytes (·10^9 L^{-1})	202 (±61; 75-379)	198 (±48; 80-327)
APTT (sec)	26.9 (±3.6; 21-48)	26.6 (±3.7; 20.0-41.8)
Fibrinogen (g L^{-1})	4.2 (±0.9; 2-6.5)	4.2 (±0.7; 2.2-5.9)
PT (s)	10.9 (±1.7; 9.1-16)	10.8 (±1.8; 9-20)

Data are n (%), mean (SD; range)

Gravity, parity and risk factors are presented as median (range)

BMI: body mass index, T1: time 1 at 500 mL and start randomization, Hb: haemoglobin, Ht: haematocrit, APTT: activated partial thrombin time, PT: partial thrombin time

Table 2 shows both primary and secondary outcomes. In the restrictive policy 51 of the 130 patients (39.2%) progressed to more than 1000 mL blood loss versus 61 of the 119 patients (51.3%) in the liberal resuscitation policy arm (difference, -12.0% [95%-CI -24.3% to 0.3%], p = 0.057). Total blood loss did not differ significantly. Mean blood loss in the restrictive arm was 1182 mL (SD 761 mL) and in the liberal arm 1242 mL (SD 621 mL), (p = 0.5).

There was no difference in haemoglobin (Hb) levels at T2, and T3 in the restrictive arm and liberal arm respectively. Hb levels < 80.6g L^{-1} at T2 and T3 are comparable in the restrictive arm and liberal arm respectively.

The number of patients in need for blood products in both groups are comparable. Packed cells were primarily given to those exceeding the 1500 mL blood loss (n = 22/25), fresh frozen plasma and fibrinogen concentrate only in those exceeding 2000 mL of blood loss, and the thrombocytes were given in a case of 6000 mL blood loss. No significant difference in coagulopathy was observed between both policies: thrombocytes < 50.10^9 L^{-1}, APTT and PT more than 1.5 times the reference range, and fibrinogen less than 1 g. The use of intrauterine balloon tamponade (n = 3/130 in the restrictive policy versus n = 2/119 in the liberal policy, p = 0.73) and the use of B lynch stitch (n = 2/130 in the restrictive policy versus n = 1/119 in the liberal policy, p = 0.61) are comparable. There was no use of arterial ligation in either group. Adverse events defined as ICU admittance, administration of more than 4 packed cells, embolization therapy, and hysterectomy were not different between both groups.

Causes identified for PPH are presented in table 3. Main cause of PPH in both groups is uterine atony; 52.3% in the restrictive arm and 63.9% in the liberal arm.

Adjustment, by means of multiple regression, for the small differences in baseline characteristics (augmentation, episiotomy, analgesics) or controlling centre of inclusion did not result in any meaningful changes in the effect estimates or in more precision.

Table 2 Primary and secondary outcomes.

	Restrictive policy (n = 130)	Liberal policy (n = 119)	p
Progression to more than 1000 mL blood loss	51 (39.2)	61 (51.3)	0.057
Total blood loss (mL)	1182 (761)	1242 (621)	0.5
Haemoglobin g L^{-1}			
T2	105.5 (15.3)	104.1 (15.6)	0.652
T3	92.7 (13.7)	99.9 (83.8)	0.849
Haemoglobin < 80.6g L^{-1} (n)			
T2	6 (4.6)	7 (5.9)	0.404
T3	18 (13.8)	18 (15.1)	0.430
Transfusion (n)			
Packed cells	14 (10.8)	11 (9.2)	0.689
Fresh Frozen Plasma	3 (2.3)	5 (4.2)	0.397
Thrombocytes	1 (0.8)	0 (0)	0.338
Fibrinogen	2 (1.5)	3 (2.5)	0.581
Coagulopathy T2			
Platelets < 50.10^9 L^{-1}	0	0	n/a
APTT > 1.5 times reference range (n (mean seconds))	3 (42.2)	4 (43.0)	0.858
PT > 1.5 times reference range (n (mean seconds))	3 (14.6)	4 (14.5)	0.880
Fibrinogen < 1 gram	0	0	n/a
Adverse events (n)			
ICU admittance	1	1	0.157
≥ 4 packed cells	1	2	0.223
Embolization	1	0	0.338
Hysterectomy	0	0	n/a

Data presented are n (%), mean (SD) unless otherwise stated

APTT: activated partial thrombin time PT: partial thrombin time ICU: intensive care unit T1: time 1 (at 500 mL blood loss and start of randomization), T2: time 2 (45-60min after T1), T3: time 3 (12-18 hours after T1)

Table 3 Causes identified for PPH

	Restrictive (n = 130)	Liberal (n = 119)
Uterine atony	68 (52.3)	76 (63.9)
Episiotomy	32 (24.6)	34 (28.6)
Retained placenta	27 (20.8)	26 (21.8)
Incomplete placenta	8 (6.2)	5 (4.2)
Cervical/vaginal trauma	17 (13.1)	11 (9.2)
Uterine rupture	3 (2.3)	0
Inversio uteri	0	0
Coagulopathy	0	0

Data are n (%)

DISCUSSION

Principal findings

A restrictive fluid resuscitation in women with mild postpartum haemorrhage could not been proven to be superior (p = 0.057), even though the confidence interval around the effect estimation ranged from decreased progression risk by almost a quarter to near equality in the risk of progression (difference, -12.0% [95%-CI -24.3% to 0.3%]). A restrictive fluid resuscitation management in women with a moderate postpartum haemorrhage does not alter the need for blood transfusion, alter coagulation parameters, or cause a rise in adverse events. A more restrictive fluid resuscitation fluid management strategy could be a safe management choice in early and mild PPH.

Results

Outside the obstetric field there is still no widely implemented consensus on fluid management in peri-operative and trauma care. As outlined in our trial protocol there is little and contradictive evidence for either liberal or restrictive fluid resuscitation regimens.[12] In addition to this outline Myles *et al.* reports an increased risk for acute kidney injury in high-risk patients during major abdominal surgery receiving a restrictive fluid management.[26] There was no difference in disability free survival in both groups. The randomized controlled trial of Myles *et al.* supports the dangers of hypoperfusion. However, their study population is a high-risk population undergoing major abdominal surgery which is not comparable to a relatively healthy obstetric population. Kwan *et al.* reports, in their systematic review of six randomized controlled trials, no evidence for or against early or larger intravenous fluid administration strategies in uncontrolled haemorrhage in trauma patients.[27] No quantitative assessment could be provided due to

diverse patient populations. They stress the necessity for further randomized controlled trials. We showed, in a systematic review, that a restrictive policy in elective surgery was favourable in comparison to a liberal fluid management policy for total complication rate, infection, and transfusion rate.[13]

The lack of consensus on perioperative fluid management is reflected in the guidelines of the American Society of Anesthesiologists (ASA) and the European Society of Anaesthesiology (ESA). ASA has not updated their perioperative fluid management since 2008.[28] In their perioperative blood management guidelines there is no mention of crystalloid or colloid use.[29] Their latest editorial note still marks the disagreement on the matter.[30] However they do agree that the optimal regimen is to replace the losses. The ESA state the lack of evidence to advice upon a perioperative fluid management. They do however advocate to avoid hypoperfusion, and advise a timely and aggressive stabilization of the cardiac preload taking a goal-directed approach.[31] However in their trauma guideline they recommend the use of a restrictive fluid management to achieve target blood pressure.[32] The ESA was also collaborator in the obstetric guideline of Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis (NATA) published in 2019. This multidisciplinary consensus statement recommends a restrictive fluid crystalloid administration of 1-2 mL crystalloids for every 1 mL blood lost.[33] This is a more liberal trend to how restrictive fluid management is generally advocated. Restrictive fluid resuscitation is based to replace the fluids lost with avoiding fluid overload.[34]

The use of colloids can impair clot function by disturbing fibrin polymerization and by faster clot disintegration. Colloids may therefore increase blood loss.[35-38] The use of starches may increase the need for blood transfusion, increase the likelihood of acute kidney injury, and overall, more side effects such as pruritis and rash.[39-41]

Systematic reviews or randomized controlled trials evaluating fluid management protocols in the obstetric population are lacking. Our trend of a favourable outcome with a restrictive fluid management policy in the obstetric field is supported by the publications of Henriquez and Gillisen.[22, 23] In a retrospective cohort study Gillisen showed deterioration in coagulation parameters correlated with the amounts of crystalloid fluids infused. Levels of haemoglobin, haematocrit, platelet count, fibrinogen, and APTT were all negatively associated with the amount of crystalloid fluids infused. Henriquez performed a retrospective cohort study on women with a severe postpartum haemorrhage, finding that administration of more than 4 L of crystalloid fluids was independently associated with more maternal adverse outcomes (a composite of mortality and severe maternal morbidity defined as hysterectomy, embolization, or ICU admittance). Mean blood loss in both studies were 3.0 and 2.9 L respectively and exceeded our mean blood loss of 1.2 L.

Clinical implications

Our study is prospective and data were gained in a randomized controlled setting. The results of this randomized controlled trial are applicable to a wide obstetric population as most women with PPH do not exceed the 1500 mL of blood loss. These data can be used to design and perform new randomized controlled trials in this fragile population and acute setting.

Strengths and Limitations

To our knowledge this is the first randomized controlled trial on fluid resuscitation strategies within the obstetric field. We reached our calculated sample size in both resuscitation arms and had no loss to follow-up for the primary outcome. Baseline characteristics were well balanced and adjustment for small differences in the baseline gave similar results.

The randomization envelopes were available at a central point at the labour ward in each location. In case of a caesarean section, an envelope was taken to the operating theatre in case the patient would reach 500 mL blood loss. The operating theatres are not at the labour ward but in a different section of the hospital at all participating locations, making it impractical to pick up an envelope from the labour ward once the patient reached 500 mL blood loss. Unfortunately, some of these unopened envelopes were disposed of during clean up instead of returned to their original central point, causing a slight imbalance of 130:122 in treatment assignments. This numerical imbalance does not influence validity. Even though we reached our aimed pre-calculated sample size, and the point estimate of the difference in risk of progression to more than 1000 mL blood loss pointed to a clinically relevant effect (absolute difference, 12.1%; number needed to treat, 9), the difference did not reach statistical significance ($p = 0.057$). With inclusion of a larger number of participants the power of study would have been higher. Arguably, in retrospect, for our sample size calculation we chose a minimally detectable relative risk that was too conservative (RR 0.5) with the consequence that smaller, but relevant, differences such as the one found would stay statistically non-significant. Pooling of our results (or data) with any similar future studies could yield more precision and enable smaller differences to be more easily detectable.

As this study was the first randomized controlled trial with a solely obstetric patient population, strict precautionary safety measures were in place. One of the main safety measures was abdication of the enrolled resuscitation arm when reaching 1500 mL blood loss. Therefore, our results can only be applied to women with a PPH less than 1500 mL blood loss, which is the majority of all women experiencing PPH. Of all women in labour,

1.4-3.9% progress to more than 1500 mL blood loss.[3, 42] Another safety measure was the choice to commence resuscitation at 500 mL of blood loss. Signs of clinical shock can present as early as 750 mL of blood loss, defined as class II haemorrhagic shock.[32] However these limitations do reduce the ability to compare the more serious adverse outcomes such as transfusion need, embolization, IC admittance and hysterectomy between these groups.

Our progression to more than 1000 mL blood loss was 39.2% in the restrictive management group and 51.3% in the liberal management group which is higher than the general percentage of women with a PPH of more than 1000 mL: 3-5.5%.[33, 42, 43] We contribute this to a selected population, we only selected women who had more than 500 mL and ongoing blood loss whereas the general percentage applies to the whole population of women giving birth. This is reflected in the percentage in the population who gave informed consent: 6.3% (102/1622) had more than 1000 mL blood loss. This is slightly higher than the reported incidences. Although important, optimal management and the safety of restrictive management or even permissive hypotension in massive PPH, concerning only a small minority of women, is not the scope of the current study. We chose to study the more common and therefore more relevant effect on the effects of fluid resuscitation in mild PPH. Adequately managing mild PPH can improve care for a large group of women and may prevent progression.

Conclusions

Although a restrictive fluid resuscitation in women with mild PPH could not been proven to be superior it does not increase the need for blood transfusion, alter coagulation parameters, or cause an increase in adverse events and therefore can be considered as an alternative treatment option. This study does not allow comments on safety on restrictive management in cases with massive PPH. More randomized controlled trials on fluid resuscitation should be conducted in patients with PPH to establish an evidence-based recommendations on this matter.

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CONTRIBUTION TO AUTHORSHIP

NL, YH, LS, and HS were involved in the conception and design of the trial. PS drafted the primary manuscript, is overall investigator of the trial, and is corresponding author. PS, HS, and LS analysed the results. MWo, JL and MWa are local investigators. All authors mentioned are collaborators in the study. All authors edited the manuscript, read and approved the final draft.

SUPPORTING INFORMATION

Supplement 1 Risk factors postpartum haemorrhage
General information
Age (> 40 years, not multiparous)
Obesity (BMI > 35)
Grand multipara
Uterus myomatosus
Other, if yes, please specify
Obstetric history
History of manual removal of placenta(l fragments)
History of PPH
Other, if yes, please specify
Current pregnancy
Anaemia (< 96·7 g/L)
Chorioamnionitis
Gestational hypertension
Multiple pregnancy
Macrosomia
Placenta praevia/accrete
Other, if yes, please specify
Current delivery
Induction of labour
Augmentation of labour
Fever in labour
Prolonged first stage of labour (> 10 hours)
Prolonged second stage of labour (> 60 minutes)
Suspected or proven placental abruption
Mediolateral episiotomy
Ventouse or forcipal extraction
Delivery by emergency caesarean section
Delivery by elective caesarean section
Retained placenta
Macrosomia (> 4 kg)
Other, if yes, please specify

BMI: body mass index PPH: postpartum haemorrhage
Other supporting information available with this article are the CONSORT 2010 checklist and the dataset. This supporting information is available upon request or at the journal's website along with the published article.

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5

Thromboelastometry in daily obstetric practice: at what amount of blood loss do we find abnormal results? A retrospective clinical observational study

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In women with postpartum haemorrhage (PPH) coagulopathy can result in life-threatening situations. Conventional laboratory testing is time consuming, generally resulting in blind non-individualized treatment according to local massive blood loss protocols.

Thromboelastometry (ROTEM®) is a visco-elastometric point of care method for testing haemostasis in whole blood which graphically shows the coagulation process from clot formation to fibrinolysis. In cardiothoracic surgery and trauma patients, thromboelastometry has been proven to be more cost-effective than conventional laboratory testing.[1] The European and American anaesthesiology guidelines recommend thromboelastometry in routine practice for massive non-obstetric haemorrhage. In this study we aimed to assess the chances of abnormal thromboelastometry results in women with PPH.

We performed a retrospective analysis of all ROTEM® (GmbH Germany) values obtained in the care for women with PPH at Maastricht University Hospital between 2014 and 2016. All women selected for the current study had given birth in hospital setting and had 500 mL and ongoing blood loss. Thromboelastometry was either performed if patients were participating in two subsequent prospective trials [2, 3] or as standard care in PPH. Both clinical studies were approved by the local Medical Ethical Committee. Written informed consent forms were collected prior to participation in the study. The clinical trial numbers are: NTR 2515 and NTR 3789.

Blood samples were taken at 500 mL blood loss. ROTEM® analysis and conventional laboratory tests were performed at the hospital laboratory. Thromboelastometry was performed in citrated whole blood using a ROTEM® delta analyser (Pentapharm, Munich, Germany). Tests were performed by trained technicians in a clinical laboratory. Quality control (internal and proficiency testing) according to the standards of ISO 15189.

We collected data from patient charts and subdivided the patients according to their eventual cumulative blood loss: less than 1000 mL, between 1000 mL and 1999 mL and 2000 mL blood loss or more. According to local PPH protocol, all blood loss was measured by weighing the absorption towels after childbirth. The first towel was disposed of directly after childbirth and not measured as this also includes amniotic fluid.

Probabilities of normal and abnormal result of the clotting time (CT) values of INTEM, EXTEM and the FIBTEM A10 values were compared between the groups. ROTEM® results were interpreted by using ROTEM® reference values in women during labour, as determined in our previous study (summarized data available as supporting information table 1).[2] All data were analysed with IBM SPSS statistics version 24™ and SAS version 9.4.

Baseline characteristics are reported in Table 1 and presented as a percentage of the total patient population or as range with a standard deviation depending on the variable presented. Data of 139 women were available for analysis. The thromboelastometric results are presented in Table 2.

Table 1 Baseline characteristics

Age (years)	32.3 (23-42 sd 4.1)
Gravidity	2 (1-8 sd 1.4)
Parity	0.7 (0-6 sd 1.0)
Gestational age (weeks)	38.5 (21.5-41.5 sd 3.1)
Gestational age (days)	272.4 (152-492 sd 29.3)
BMI (m^2)	25 (17-48 sd 5.1)
Vaginal delivery (n)	62 (44.6%)
Ventouse delivery (n)	28 (20.1%)
Planned caesarean (n)	27 (19.4%)
Unplanned caesarean (n)	21 (15.1%)
Manual placental removal (n)	24 (17.4%)
Curettage for placental remnants (n)	4 (2.9%)

Overall n = 139, (range or percentage), sd: standard deviation

Table 2 ROTEM® results per blood loss range

	500-999 mL Number (% [95%-CI])	**1000-1999 mL Number (% [95%-CI])**	**≥2000 mL Number (% [95%-CI])**
INTEM CT abnormal	1/64 (1.6 [0.3-8.3])	0/35 (0 [0-9.9])	0/20 (0 [0-16.1])
EXTEM CT abnormal	3/65 (4.6 [1.6-12.9])	1/35 (2.9 [0.5-14.5])	3/20 (15 [5.2-36.0])
FIBTEM A10 abnormal	1/65 (1.5 [0.3-8.2])	1/34 (2.9 [0.5-14.9])	4/20 (20 [8.1-41.6])

95%-CI: 95% confidence interval

For women with less than 1000 mL blood loss the chance of an abnormal ROTEM® INTEM CT result was 1.6% (95% CI [0.3-8.3]), of an abnormal EXTEM CT result 4.6% (95% CI [1.6-12.9]), and of an abnormal result of the FIBTEM A10 1.5% (95% CI [0.3-8.2]). Among women with blood loss between 1000 and 1999 mL, we saw abnormal INTEM CT results in 0% (95% CI [0-9.9]) of the cases, abnormal EXTEM CT in 2.9% (95% CI [0.5-14.5]), and abnormal FIBTEM A10 in 2.9% (95% CI [0.5-14.9]) of the cases. Among those with blood loss of 2000 mL or more we found 0% abnormal results for the INTEM CT (95% CI [0-16.1]), 15% for EXTEM CT (95% CI [5.2-36.0]) and 20% for FIBTEM A10 95% CI [8.1-41.6]).

Our results show that among women with less than 1000 mL blood loss, FIBTEM A-10 has a 98.5% chance to fall within the reference limits, for INTEM CT and EXTEM CT this is 98.4% and 95.4%. The likelihood of an abnormal INTEM CT or EXTEM CT is comparable to the likelihood of an abnormal FIBTEM A-10 result under 2000 mL blood loss. This might support the fact that prophylactic fibrinogen supplementation is not effective.[4]

We observed some unexpected abnormal EXTEM results in women with less than 1000 mL blood loss. These cases were scrutinized but we had no explanation for these outliers. EXTEM is influenced by fibrinogen, platelets and extrinsic coagulation factors especially FVII. FVII has the shortest half-life and one of the lowest plasma concentrations but is used as first step to form the FVII-TF complex. This might explain the abnormal EXTEM results with normal FIBTEM and INTEM values.

Our results confirm previously published data showing an increased likelihood of abnormal ROTEM® results increases in women with more blood loss. [5] However this was not restricted to FIBTEM and more than 80% of women had normal coagulation results.

Current guidelines advocate to perform conventional laboratory testing including haemostasis as early as 500 mL blood loss (RCOG) and at 1000 mL (The Dutch Society of Obstetrics and Gynaecology, NVOG). Restricting testing to women at 1000 mL would reduce testing with about 70% as compared to testing at 500 mL.

In obstetric guidelines, thromboelastometry analysis is not yet widely implemented. A recent review recommends monitoring haemostasis with either standard coagulation tests or point-of care testing (TEM analysis) in the course of PPH, acknowledging the limited data available on this subject.[6] Snegovkikh *et al.* performed a retrospective study on point-of-care testing showing a significant reduction in use of blood products, intensive care admission rate and hospital stay. This reduction contributed to reduced hospitalization costs well over $17.000 dollars per patient with severe postpartum haemorrhage (≥ 1500 mL blood loss).[7]

To our best knowledge there are no previous publications on trying to determine the best timing for point-of-care laboratory tests on haemostasis in women with postpartum haemorrhage.

There are some important limitations to this study. As this is a retrospective study selection and information bias cannot be excluded. Our sample size is too low, particularly for women with more than 2000 mL blood loss, to be able to draw firm conclusions about the optimal timing for testing haemostasis in women with PPH. Furthermore,

thromboelastometry blood results were not collected at the exact same amount of blood loss and the aetiology of the haemorrhage is divers. We have limited data on fluid resuscitation and its potential influence on the results due to lack of reporting.

There is scarce literature and currently no feasible study design to provide us with more data on when to perform thromboelastometry in women with ongoing PPH. We emphasize that the chance of abnormal results below 2000 mL is very small. Our results warrant further study with a prospective design.

To conclude; in women with PPH between 500 - 2000 mL blood loss the likelihood of any abnormal ROTEM® result was 1.5-4.6%. Unlike previous studies we observed abnormal results other than only FIBTEM. We advocate that when thromboelastometry is performed, this should include all pathways. In women with blood loss of 2000 mL or more, at least 80% have normal coagulation parameters measured by thromboelastometry. Therefore, standard administration of coagulative agents other than tranexamic acid is likely to be unnecessary. It should be avoided unless the blood loss is massive and awaiting test results is not feasible. There is no one-size-fits all protocol in the treatment of women with vital PPH and treatment should be individualized per patient, which could be facilitated by thromboelastometry.

DISCLOSURE OF INTERESTS

None of the authors have relevant financial, personal, political, intellectual or religious interests to disclose.

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CONTRIBUTION TO AUTHORSHIP

Pim Schol: This author helped with the conception and design, analysis and interpretation of data, revising the article and approving final manuscript.

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6

Restrictive versus liberal fluid administration strategy (REFILL study) in postpartum haemorrhage: effects on thromboelastometry (ROTEM™) values, a randomized controlled trial

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ABSTRACT

Objective

Current obstetric guidelines for postpartum haemorrhage (PPH) vary in fluid resuscitation management due to scarce literature on this subject. In the present study, we evaluated the effect of restrictive versus liberal fluid management on thromboelastometry and coagulation parameters in early PPH.

Study design

The present study was part of the REFILL study, a randomized controlled multicentre trial from August 2014 till September 2019. Women who gave consent were randomized at 500 mL and ongoing blood loss in the third stage of labour to either a restrictive fluid administration policy (RFA) receiving clear fluids 0.75 to 1.0 times the blood lost or a liberal fluid administration policy (LFA), receiving 1.5 to 2.0 times the blood lost. In 72 patients (36 in either group), thromboelastometry through a ROTEM™ panel was performed: just after randomization and 45 to 60 min after randomization. We evaluated within-group and between-group differences over time in EXTEM clotting time (EXTEM CT), EXTEM amplitude at 10 minutes (EXTEM A10), INTEM clotting time (INTEM CT), AND FIBTEM amplitude at 10 minutes (FIBTEM A10). We evaluated the average values of Clauss fibrinogen, Activated Partial Thromboplastin Time (APTT), and Partial Thromboplastin time (PT) in the total study population.

Results

Mean fluid administration was 1214 mL (SD 1250 mL) and 1588 mL (SD 982 mL) in the RFA and LFA group, respectively. Mean blood loss in the RFA group was 1307 mL (SD 728 mL), mean blood loss in the LFA group was 1055 mL (SD 376 mL). At T2, there were no significant differences in the mean ROTEM™ values between the women in the two study arms for any of the four ROTEM™ parameters after correction for baseline value in change over time. No significant differences were seen between the two randomized groups regarding thrombocytes, fibrinogen, APTT, and PT parameters.

Conclusion

In women with postpartum haemorrhage less than 1500 mL we found no clinically relevant impact of restrictive or liberal fluid administration strategy on thromboelastometric haemostatic and regular coagulation parameters.

INTRODUCTION

An important aspect in the management of postpartum haemorrhage is fluid resuscitation. In the available obstetric guidelines, there is no uniformity in fluid resuscitation strategy. The Royal College of Obstetricians and Gynaecologists (RCOG) Green Top guideline states to commence fluid resuscitation at 500 mL blood loss. If blood loss reaches 1000 mL or if a patient shows signs of clinical shock the RCOG recommends to infuse up to 3.5 L of clear fluids.[1] The American College of Obstetricians and Gynecologists (ACOG) do not mention clear fluid transfusion, their practice guideline mentions to prepare for blood(product) transfusion in women with more than 1500 mL blood loss and abnormal vital signs.[2] The Dutch society of obstetricians and gynaecologists (NVOG) states that there is currently no evidence to administer more fluids than lost when reaching 500 mL of blood loss.[3]

Volume resuscitation can consist of crystalloids, colloids, transfusion of blood products, or a combination of either. All have their (dis)advantages. Crystalloids and colloids are readily available and can be transfused fast. Yet large amounts may induce coagulopathy, hypothermia, and acidosis causing the classic lethal triad.[4-6] Blood transfusion might impose a variety of blood transfusion related risks such as antibody formation, acute haemolytic reaction, anaphylactic shock, acute lung injury related to transfusions (TRALI), and transfusion-related circulatory overload (TACO).[7]

To evaluate haemostasis, standard plasma assays, such as fibrinogen, Activated Partial Thromboplastin Time (APTT) and Partial Thromboplastin time (PT), as well as thromboelastometry can be used. Thromboelastometry is a dynamic, whole blood, viscoelastic coagulation test which evaluates the coagulation from clot formation throughout fibrinolysis.[8] It provides real time information on the intrinsic and extrinsic coagulation pathway, as on the platelet and fibrinogen contribution to the clot.[8] Thromboelastometry can be used within the obstetric field with slightly adjusted reference ranges compensating for the haemostatic changes in pregnancy and childbirth.[8, 9]

In a randomized controlled trial (RCT) we previously showed no disadvantages to a restrictive fluid administration policy (RFA) in early stages of PPH on the progression of blood loss.[10] In this paper we present a pre-planned subgroup of patients from the RCT in whom we evaluated the effect of restrictive and liberal fluid administration policy on coagulation in women with a postpartum haemorrhage less than 1500 mL. We hypothesized prolonged coagulation time (CT) values and decreased A10 values with a liberal fluid administration policy based upon the coagulopathy induced by large crystalloid and colloid infusion.

METHODS

REFILL was a randomized controlled multicentre trial from August 2014 till September 2019. REFILL ran in four hospitals in the Netherlands. The study was approved by the Medical Ethics Committee Maastricht University Medical Center (approval number; NL4294206813). This trial is registered in the Netherlands Trial Register NTR3789 or NL3623. (https://www.trialregister.nl/trial/3623)

Women were considered eligible if they were 18 years and over, were pregnant and labour started after 24+0 weeks of pregnancy, understood the Dutch language, and were mentally competent. Vaginal and caesarean deliveries were both included. Women were excluded if they used prophylactic or therapeutic anticoagulant therapy (carbasalate calcium within the previous 10 days or low molecular weight heparins within the previous 48 h), known coagulation disorders, pre-eclampsia, contraindication for liberal fluid therapy (e.g., cardiac causes, systemic causes such as Marfan syndrome, renal causes, or pulmonary failure), or antenatal diagnosis of placenta accrete spectrum. We obtained written informed consent prior to active labour and oral confirmation during early labour from each patient.

Randomization was performed through sealed opaque envelope by the treating team of health care professionals. Randomization was stratified per centre in blocks of four in an 1:1 allocation. The sealed opaque envelopes were created by an independent research nurse or medical student not involved in the randomization of the patient. Envelopes were distributed per centre by Maastricht University Medical Center.

Women who gave written and oral consent were randomized at 500 mL and ongoing blood loss in the third stage of labour to either a restrictive fluid administration policy (RFA) or a liberal fluid administration policy (LFA). In the RFA group patients received clear fluids at 0.75 to 1.0 times the blood lost, in the LFA group patients received clear fluids at 1.5 to 2.0 times the blood lost. The first 2000 mL of volume replacement consisted of NaCl 0.9%, Ringer's lactate, or a combination of both. Blood loss was measured by weighing the absorption towels with exclusion of the first absorption towel which was disposed directly after birth of the child.

In the study citrated (3,2%) and EDTA blood samples (Vacutainer, BD) were drawn at three moments: T1, and T2. T1 was at 500 mL and ongoing blood loss, patients were randomized and the first blood sample was drawn. If there was no intravenous access yet, an intravenous access was established. From this blood sample a haemoglobin concentration, haematocrit, platelet count (Sysmex XN-9100, Cell Dyn Sapphire or Advia

21202i), activated partial thromboplastin time (Siemens CS2100 with Actin FSL, STA-R Evolution with STA APTT or STA-R Max with C.K. Prest), prothrombin time (Siemens, CS2100 with Innovin, STA-R Evolution with Neoplastin plus or STA-R Max with Neoplastin plus), and Clauss fibrinogen (Siemens CS2100 with Innovance or STA-R Evolution with STA Fibrinogen) were measured. A subset of 72 women who delivered in Maastricht University Medical Center or Zuyderland Medical Center thromboelastometry a ROTEM® panel (Werfen, ROTEM Delta) was performed. ROTEM values were procured in subsequent randomizations at the T1 and T2 times as the regular samples were drawn, regardless of the amount of blood loss or randomization. The other participating centres had no ROTEM® analysis available.

Fluid resuscitation was initiated at T1. At T2, 45-60 min after T1, a second set of blood samples were drawn. Parameters measured were identical as in T1. At T3, 12-18 h postpartum, a third blood sample was drawn if the patient was still in the hospital with haemoglobin and haematocrit. Moment T3 was not used for these analyses.

Hemodynamic parameters such as blood pressure, heart rate and oxygen saturation were measured according to local protocol. In case of a systolic blood pressure < 90 mmHg, diastolic blood pressure < 50 mmHg, a decrease of more than 20 mmHg in blood pressure, or a maternal heartrate of 125 beats per min of more, additional 500 mL of clear fluid was administered in 15 min in either group.

The underlying cause of the postpartum haemorrhage was treated according to national and local protocol (Dutch Society of Gynaecology and Obstetrics, NVOG). If 1500 mL blood loss was reached the randomized study arm was abandoned and patients were treated according to the local massive haemorrhage protocol. Blood samples were still drawn and patient data was analysed according to intention to treat.

Data were collected from patient charts and study files, and stored anonymously in Maastricht University Medical Centre in a restricted access file. A trial number was assigned to each patient at randomization. Severe adverse outcomes (SAE) were defined as the need of intensive care admittance, the need of four or more units of packed cells, embolization, and hysterectomy. SAE were registered and analysed by a data safety monitoring board. Throughout the study there was no need to abandon the trial prematurely.

Results regarding the primary outcome of the REFILL study have been published previously.[10] The secondary outcome was differences in coagulation parameters. One in ROTEM® values defined as the difference in EXTEM clotting time (EXTEM CT), EXTEM

amplitude at 10 min (EXTEM A10), INTEM clotting time (INTEM CT), AND FIBTEM amplitude at 10 min (FIBEM A10) at T2 in the subset of 72 patients. Secondly the difference standard plasma assays of APTT, PT and fibrinogen in the total study population at T2. Correction for baseline and change over time between T1 and T2 was calculated.

Comparative analysis was performed with either a Students' *t* test for continuous data or the chi-square (Fishers' exact) test for dichotomous outcomes. To compare between group differences in change over time, linear regression was performed with adjustment for the baseline value of the outcome under analysis. Data were analysed according to intention to treat. All analyses were performed by means of IBM SPSS 24.0 software.

RESULTS

Of a total of 72 patients, 36 patients were randomized to the RFA group and 36 patients to the LFA group. The baseline characteristics are presented in table 1.

Mean fluid administration was 1214 mL (SD 1250 mL) and 1588 mL (SD 982 mL) in the RFA and LFA group, respectively. Mean blood loss in the RFA group with available ROTEM values was 1307 mL (SD 728 mL), mean blood loss in the LFA group with available ROTEM values was 1055 mL (SD 376 mL). Nine patients reached more than 1500 mL blood loss; 3 in the LFA and 6 in the RFA. These patients were treated according to local massive haemorrhage protocol.

Unfortunately, data on thromboelastometric parameters was not available for all 72 patients. Data was unavailable in case of a shortage of blood drawn to perform the complete ROTEM® panel. Table 2 presents the available data.

At T2 there were no differences in the mean ROTEM® values between the women in the two study arms for EXTEM CT, EXTEM A10, INTEM CT and FIBTEM A10. In the LFA group, we found a statistically significant difference in average FIBTEM A10 values at T1 and T2 of 1.43mm ($p = 0.041$). None of the other ROTEM values in the LFA group, and none of the ROTEM values in the RFA group showed any statistically significant change between T1 and T2. After correction for baseline values there were no significant differences between the randomized groups in change over time (table 2).

Table 1 Baseline patient characteristics

	Restrictive (RFA)	Liberal (LFA)
Age (years)	32.7 (3.6)	32.6 (4.6)
BMI	25.9 (6.3)	25.2 (4.6)
Gestational age (weeks)	38.6 (2.5)	39.0 (2.0)
Gravidity	2.4 (1.5)	2.1 (1.1)
Parity	0.94 (0.98)	0.75 (0.69)
Gestational age (days)	271 (17)	274 (14)
Risk factors HPP (amount)	3.6 (2.0)	3.3 (1.5)
History of:		
Manual removal of placenta	4 (11%)	1 (2.8%)
Postpartum haemorrhage	7 (20%)	5 (14%)
Blood transfusion with postpartum haemorrhage	3 (8.3%)	1 (2.8%)
Onset of labour		
Spontaneously	6 (17%)	5 (14%)
Induction	20 (56%)	22 (61%)
Caesarean, planned	9 (25%)	10 (28%)
Outcome		
Delivery		
Spontaneously	19 (53%)	18 (50%)
Ventouse	6 (17%)	4 (11%)
Caesarean	11 (31%)	14 (39%)
T1 laboratory parameters		
Hb (g/L)	112.8 (16.1)	114.4 (12.6)
Ht (%)	0.34 (0.04)	0.35 (0.04)
Thrombocytes ($x10^6/mm^3$)	213 (66)	195 (54)
APTT (sec)	26.3 (5.0)	25.6 (3.1)
Fibrinogen (g/L)	4.2 (0.7)	4.4 (0.5)
PT (sec)	10.0 (0.5)	9.9 (0.5)
T1 ROTEM® values		
EXTEM CT (sec)	55.36 (6.76)	57.04 (9.79)
EXTEM A10 (mm)	62.10 (8.14)	62.71 (4.75)
INTEM CT (sec)	135.91 (22.52)	137.40 (22,74)
FIBTEM A10 (mm)	20.57 (5.26)	21.72 (3.41)

Data are n (%), mean (SD)

BMI: body mass index, T1: time 1 at 500 mL and start randomisation, Hb: haemoglobin, Ht: haematocrit, APTT: activated partial thrombin time, PT: partial thrombin time, CT: coagulation time, A10: firmness after 10 minutes, SD: standard deviation, RFA: restrictive fluid administration, LFA: liberal fluid administration.

We evaluated the average values of fibrinogen, APTT, and PT in the complete study population (n = 249) at T2 between the randomized groups. For fibrinogen data was available in 99 cases in the RFA group and in 88 cases in the LFA group. The mean fibrinogen level at T2 was 3.98 g/L in the RFA group and 3.84 g/L in the LFA group (p = 0.26). For APTT data was available in 102 cases in the RFA group and in 90 cases in the LFA group. Mean APTT at T2 was 27.54 seconds in the RFA group versus 27.59 seconds in the LFA group (p = 0.93). Data on PT values at T2 was available in 90 cases in the RFA group and in 80 cases in the LFA group. Mean PT at T2 was 10.90 seconds versus 10.90 seconds (p = 0.97) for both study groups. Data on thrombocytes at T2 was available in 108 cases in the RFA group and in 91 cases in the LFA group. Mean thrombocyte levels at T2 was 204.0 x 10^9/L in the RFA group versus 198.8 x 10^9/L in the LFA group. Linear regression with correction for baseline values at T1 showed no significant effect of fluid resuscitation policy for fibrinogen, APTT, PT and thrombocyte values (table 3).

Table 2 Mean ROTEM® values and change over time at T1 and T2

	EXTEM CT (s)		**EXTEM A10 (mm)**		**INTEM CT (s)**		**FIBTEM a10 (mm)**	
	RFA n = 25	**LFA n = 24**	**RFA n = 21**	**LFA n = 21**	**RFA n = 21**	**LFA n = 21**	**RFA n = 21**	**LFA n = 21**
T1, mean	55.48	57.00	60.76	62.61	135.76	138.14	20.43	21.48
T2, mean	54.92	56.79	61.48	62.00	141.62	143.14	19.86	20.05
Change over time, mean	-0.56	-0.20	0.71	-0.62	5.86	5.00	-0.57	-1.43
Effect controlling for baseline (T1) value								
Beta, RFA versus LFA	-1.08 [-4.48 to 2.32]		0.34 [-4.01 to 4.69]		-0.71 [-14.07 to 12.66]		0.54 [-1.69 to 2.78]	

In the RFA group both T1 and T2 values were present in 25 patients for EXTEM CT and 21 for EXTEM A10, INTEM CT, and FIBTEM A10. In the LFA group both T1 and T2 data was available for 24 in the EXTEM CT group and 21 for the EXTEM A10, INTEM CT, and FIBTEM A10.
Reference ranges coagulation values peri-partum: fibrinogen (g/L): 3.6-6.8, APTT (mm): 24-34 (MUMC, Zuyderland UMCN); 26-36 sec (JBZ), PT (s): 9.6-10.4 (MUMC and Zuyderland); 12.0-17.8 (UMCN); 12.0-15.0 (JBZ).
RFA = restrictive fluid administration, LFA = liberal fluid administration, 95%-CI = 95%-Confidence interval, T1 = time 1, at 500cc blood loss and randomization, T2 = time 2, 45-60minutes after T1.9, APTT = activated partial thrombin time, PT = partial thrombin time, MUMC = Maastricht University Hospital, UMCN = University Medical Center Nijmegen, JBZ = Jeroen Bosch Hospital.

Table 3 Mean coagulation values and change over time at T1 and T2

	Fibrinogen (g/L)		APTT (s)		PT (s)		Thrombocytes (10^9/L)	
	RFA n = 99	LFA n = 88	RFA n = 102	LFA n = 90	RFA n = 90	LFA n = 80	RFA n = 108	LFA n = 91
T1, mean	4.23	4.25	26.93	26.58	10.88	10.79	201.8	198.8
T2, mean	3.98	3.84	27.54	27.59	10.90	10.90	204.0	196.9
Change over time, mean	-0.25	-0.41	0.61	1.01	0.02	0.11	-2.2	1.9
Effect controlling for baseline (T1) value								
Beta, RFA versus LFA	-0.17 [-0.37 to 0.31]		0.52 [-0.67 to 1.71]		0.05 [-0.21 to 0.31]		-3.14 [-11.40 to 5.12]	

In the RFA group T1 and T2 values were present in 99 patients for fibrinogen, 102 for APTT., and 90 for PT. In the LFA group T1 and T2 data was available for 88 for fibrinogen, 90 for APTT, and 80 for PT. Reference ranges coagulation values peri-partum: fibrinogen (g/L): 3.6-6.8, APTT (mm): 24-34 (MUMC, Zuyderland UMCN); 26-36 sec (JBZ), PT (s): 9.6-10.4 (MUMC and Zuyderland); 12.0-17.8 (UMCN); 12.0-15.0 (JBZ).

RFA = restrictive fluid administration, LFA = liberal fluid administration, 95%-CI = 95%-Confidence interval, T1= time 1, at 500cc blood loss and randomization, T2 = time 2, 45-60minutes after T1.9, APTT = activated partial thrombin time, PT = partial thrombin time, MUMC = Maastricht University Hospital, UMCN = University Medical Center Nijmegen, JBZ = Jeroen Bosch Hospital.

DISCUSSION

We showed no significant differences in plasma and whole blood coagulation parameters between a restrictive fluid administration policy and a liberal fluid administration policy in women with a postpartum haemorrhage less than 1500 mL. Mean ROTEM® values at T1 and T2 were well within refence ranges in pregnancy.[9]

The strength of our study is the randomized controlled design of the study and the adherence to the study protocol. In the restrictive group 0.93 times the blood loss was replenished compared to 1.5 times in the liberal group. An important limitation of our study is the limited number of patients evaluated. Even though this was a multicentre study not every hospital has adopted a ROTEM™ analysis in the management of postpartum haemorrhage. The subset analysis is underpowered; therefore, we analysed the available data on fibrinogen, APTT, PT, and thrombocyte values in the complete study group at T2 as derivative representation of the fibrinogen, intrinsic and extrinsic pathway status respectively. Standard laboratory coagulation test have a correlation with the ROTEM™ results. EXTEM CT is correlated to PT results, INTEM CT to APTT results and FIBTEM

A5, A10, and maximum clot firmness (MCF) to Clauss fibrinogen results. Platelet count influences clot stability, measured by INTEM and EXTEM.[9, 11-13] Our results showed no significant differences in fibrinogen, APTT, and PT levels between both groups. Linear regression correcting for baseline value showed little and non-significant impact of fluid administration policy in early postpartum haemorrhage. Limitation of this analysis is inter-centre differences in PT time analysis. The reference range of a PT time analysis in MUMC and Zuyderland are 9.6-10.4 seconds, whereas the reference range of PT time analysed in University Medical Center Nijmegen (UMCU) and Jeroen Bosch Hospital (JBZ) is different with 12.0-17.8 seconds and 12.0-15.0 seconds respectively. However mean PT times do not exceed 11 seconds and stay therefore well within 1.5 times the upper limit of the smallest reference range.

The confidence interval ranges of all parameters analysed are small, and if the extremes of these intervals would hold, these values would not indicate clinically relevant differences. This suggests that the aforementioned ROTEM® parameters are not affected by a restrictive or a liberal fluid administration policy in early postpartum haemorrhage as performed in this study.

We did not find any clinically relevant differences between RFA and LFA in women with PPH up to 1500 mL regarding coagulation parameters. Our data are limited by the amount of blood loss. Fluid resuscitation protocols and the effect on coagulation might become more relevant when larger amounts of clear fluids are transfused at greater amounts of blood loss. This hypothesis is underlined by a large retrospective cohort study by Gillisen in which 1038 women with severe PPH were analysed for amount of infused clear fluids and the differences in haemostatic parameters.[14] Gillisen *et al.* showed a more severe deterioration of coagulation parameters with administration of larger volumes of clear fluids. More prospective research is needed to evaluate the effect of resuscitation strategies on coagulation parameters in the population with more than 1500 mL of blood loss.

In conclusion, we found no meaningful impact of fluid resuscitation strategy on thromboelastometry haemostatic parameters and traditional coagulation parameters in women with postpartum haemorrhage less than 1500 mL. Future studies are needed to evaluate the impact of fluid resuscitation on coagulopathies in severe postpartum haemorrhage.

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7

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

The focus of this thesis was to evaluate existing treatment protocols regarding clear fluid resuscitation policy during postpartum haemorrhage, with the aim to improve the evidence base for the care of women with postpartum haemorrhage.

Within the obstetric field, recommendations regarding fluid resuscitation policy are generally based upon literature from outside the obstetric field. At the start of writing this thesis, guidelines advised to administer almost twice the amount of blood lost as fluid resuscitation in patients with post-partum haemorrhage. The guidelines were often based upon inadequately evaluated textbook management strategies formed in the 1960s based upon Shires's proposed third space losses.[1, 2] Unevaluated strategies could potentially harm patients. This is exactly why we started the work described in this thesis.

In chapter 2 we present a systematic review with meta-analysis comparing a liberal fluid management policy to a restrictive management policy during elective surgery outside the obstetric field. We analysed the results of 12 randomised controlled trials performed during any elective surgery. This meta-analysis contains 1397 patients (693 in the restrictive protocol and 704 in the liberal protocol). Overall, the liberal group received more fluids compared to the restrictive group (mean 4048 mL (2928 - 5775 mL) versus mean 2019 mL (997.5 – 3517 mL) respectively. Meta-analysis showed that, overall, in the restrictive group, compared to the liberal group, fewer patients experienced a complication (RR 0.65, 95%-CI [0.55-0.78]). The total complication rate (RR 0.57, 95%-CI [0.52-0.64]), risk of infection (RR 0.62, 95%-CI [0.48-0.79]) and transfusion rate (RR 0.81, 95%-CI [0.66-0.99]) were also lower in the restrictive management group. The incidence of postoperative rebleeding did not differ between both groups: 1.5% in the restrictive group compared to 2.31% in the liberal group, RR 0.76 (95%-CI [0.28-2.06]). Restrictive fluid management policy in comparison to a liberal fluid management policy during elective surgery generally led to a 35% reduction in patients with a complication, a lower infection rate, and a lower need for blood transfusion.

In chapter 3, we present our randomised controlled trial protocol. In this chapter we first analyse the available evidence and guidelines regarding clear fluid resuscitation. All of the studies found were performed outside the obstetric patient population; controlled hypotensive resuscitation has been investigated in animal studies, military settings, and non-pregnant trauma patients. These studies might show an advantage in regard to restrictive fluid resuscitation. However, very few well-performed randomised controlled trials are available to substantiate the suggested advantage. We therefore conclude that,

based on these non-obstetric sources, there is little and contradictory evidence for either a restrictive or a liberal fluid resuscitation approach. These findings were the rationale behind our randomised trial protocol presented in chapter 3.

In chapter 4, to answer the question whether there is an advantage for either a restrictive fluid policy in comparison to a liberal fluid policy within our own patient population, we carried out a randomised controlled trial (RCT). With this RCT we evaluated whether a more restrictive fluid resuscitation policy in early postpartum haemorrhage at 500 mL reduces the risk of progression towards a severe postpartum haemorrhage (≥ 1000 mL). The design and methods of the RCT are outlined in chapters 3 and 4. In short: in four Dutch hospitals, pregnant patients were recruited in the period August 2014 to September 2020. The patients were asked informed consent to participate in case of 500 mL and ongoing blood loss in the third stage of labour. The patients were randomised to a restrictive fluid administration policy (clear fluids 0.75 – 1.0 times the volume of blood lost) or a liberal fluid administration policy (clear fluids 1.5 – 2.0 times the volume of blood lost). In total of 252 patients were randomised, 130 to the restrictive resuscitation group and 122 to the liberal resuscitation group. In the restrictive management group 51 of the 130 patients (39.2%) progressed to more than 1000 mL blood loss versus 61 of the 119 patients (51.3%) in the liberal management group (difference, -12.0%, 95%-CI [-24.3% to 0.3%], p = 0.057). There was no difference in the need for blood transfusion, coagulation parameters, or in adverse events between the groups.

In chapter 5, we sought to establish the best timing for point-of-care laboratory testing on haemostasis in patients with postpartum haemorrhage as haemostasis combined with timely, adequate correction of haemostasis can aid optimal management of PPH. We performed a retrospective analysis on data available from patients in regular postpartum care, patients who participated in an earlier thromboelastometry study during pregnancy and labour [3], and patients who were included in the REFILL study. The probability of an abnormal rotational thromboelastometry (ROTEM®) result in patients with PPH between 500 – 2000 mL was 1.6% (95% CI [0.3-8.3] for INTEM clotting time (CT), 4.6% (95% CI [1.6-12.9] for EXTEM CT, and 1.5% (95% CI [0.3-8.2] for FIBTEM A10. In patients with blood loss of ≥ 2000 mL at least 80% had normal thromboelastometric parameters. On the basis of our findings, we note that standard administration of coagulative agents other than tranexamic acid is likely unnecessary. There is no one-size fits all protocol in the treatment of vital PPH and treatment should be individualised per patient which can be facilitated by thromboelastometry. We did not evaluate the effect of fluid resuscitation policy on the thromboelastometric parameters in this analysis.

In chapter 6, we evaluated the effect of the restrictive and liberal resuscitation protocols as performed in our RCT on thromboelastometry parameters and elaborated the analyses on regular haemostatic parameters. ROTEM® analysis was performed in a subgroup of our original RCT population: 72 patients. We found no clinically relevant impact of fluid resuscitation policy on thromboelastometric parameters in our study population. Additional analysis on thrombocytes, fibrinogen, APTT, and PT parameters between the fluid resuscitation policies in the complete trial group revealed no additional impact of fluid administration strategy in postpartum haemorrhage < 1500 mL.

The results of our RCT show no statistically significant difference in outcome for a restrictive fluid management compared to a liberal fluid management in mild postpartum haemorrhage, or an effect of either fluid management on coagulation parameters (chapter 4 and 5). In addition, there is very little and contradictive evidence for a liberal fluid management outside the obstetric field as outlined in chapter 2 and 3. We therefore conclude there is no disadvantage in a more restrictive approach.

Research published in 2018 and 2019 by Gillisen *et al.*[4] and Henriquez *et al.*[5] indicates that a liberal resuscitation approach does affect the outcomes negatively in severe postpartum haemorrhage. Retrospective research performed by Gillissen *et al.* showed that the administration of clear fluids in larger volumes is associated with worsening of coagulation parameters. They reviewed a retrospective cohort of 1038 patients experiencing severe postpartum haemorrhage with the need for transfusion of at least 4 packed cells or packed cells with the addition of fresh frozen plasma or platelets. In patients receiving more than 3.5 L of clear fluids a more severe deterioration of haemoglobin, platelet, APTT, and fibrinogen levels was shown when compared to patients receiving less than 2 L. Groups were stratified for blood loss. Henriquez *et al.* determined in a retrospective cohort evaluation that administration of more than 4 L of clear fluids is independently associated with a composite of severe maternal outcomes defined as maternal mortality, hysterectomy, arterial embolization, and intensive care admittance. Mean blood loss in this cohort group was 3.0 L.

In our systematic review in chapter 2 we found, despite the comparable mean blood loss between the groups, more need for blood transfusion in the liberal group. In our RCT we did not see a difference in blood transfusion between both groups. We can explain this difference between the systematic review and RCT in protocols used. In our randomised controlled trial we linked the amount of clear fluid transfusion to the amount of blood loss. In the systematic review there was a difference in amount of clear fluids transfused, namely per mL/kg/hr, therefore a patient with minimal blood loss would receive more clear fluids than a patient with significant (e.g., 800 mL) blood loss in our trial. Mean

fluid administration in the systematic review was 2019 mL in the restrictive group versus 4048 mL in the liberal group in comparison to mean blood loss of 343 mL in the restrictive group versus 372 mL in the liberal group. This would suggest that haemodilution could be a key factor in adverse outcomes related to clear fluid administration. It would also account for why we did not find a difference in haemostatic parameters as presented in chapter 6 and why Gillissen *et al.* and Henriquez *et al.* did find this difference in their research.

Given that we do not show a disadvantage when a restrictive fluid policy is adopted in mild postpartum haemorrhage, and the possible harm of a liberal fluid policy shown by Gillisen *et al.* and Henriquez *et al.,* we conclude that a restrictive fluid resuscitation management based on replacing the lost blood volume with an equal volume of clear fluids should be adopted in postpartum haemorrhage care.

METHODOLOGICAL ISSUES

The REFILL trial was the first RCT within the obstetric population analysing the effect of fluid resuscitation on mild postpartum haemorrhage. A randomised controlled trial is a strong research method however as this research was performed in an acute setting, double blinding was not possible. As is often the case in studies in the acute setting, adherence to blood withdrawal was not always possible on the exact moment or at all. Therefore, we chose progression to more than 1000 mL as our primary outcome rather than laboratory values that might be more strongly indicative, but do not fit the acute situation.

We limited the blood loss in this trial to 1500 mL. This is the first RCT on this subject within the obstetric population, and in other fields there are still limited numbers of RCT's on the matter. Therefore, in regard to patient safety, the randomised arm was abdicated at 1500 mL of blood loss and local massive haemorrhage protocol was followed. Despite this limitation, the majority of patients will remain below that threshold as of all patients in labour 1.4-3.9% will progress to more than 1500 mL blood loss.[6, 7] This makes our trial applicable for the majority of labouring patients.

We did not reach statistically significant results (p = 0.057) in more progression to > 1000 mL in the liberal group, even though the absolute difference was -12.0% (95% CI [-24.3-0.3], corresponding to a number needed to treat (NNT) of 9. The boundaries of our 95% confidence interval suggest near equality to nearly a quarter reduction in the risk of progression, which would be clinically relevant. If one would evaluate our RCT for a liberal

fluid resuscitation policy, statistically a liberal fluid policy is not different in comparison to a restrictive approach. However, the 95%-CI does cross a clinical decision threshold that dictates recommending a restrictive approach. Therefore, the evidence for a liberal approach would be downgraded according to GRADE evaluation.[8] In retrospect, we chose a minimally detectable relative risk ratio that was too optimistic (RR 0.5). Pooling our data with similar (future) studies could yield more precision. A factor of influence might be the actual mean add back in the liberal fluid policy group. In the restrictive management arm the mean fluid administration was 1078 mL and mean blood loss 1182 mL, which is a mean add back of 0.91 times of the volume lost. In the massive management arm the mean fluid administration was 1534 mL and mean blood loss 1242 mL, which is a mean add back of 1.24 times of the volume lost. The mean volume replenished in the massive resuscitation arm is less than the 1.5-2.0 times the protocol advised. This may indicate an even stronger advantage for the restrictive resuscitation policy than seen in our results. We explain less adherence to the massive fluid resuscitation protocol by the growing knowledge that a massive fluid protocol may harm the patient. As such, the rationale for this study may have caused a Hawthorne effect in the treating physicians.

IMPLICATIONS FOR DAILY PRACTICE

PPH incidence is rising globally as described in our introduction. Multiple explanations can be found as to why this incidence is rising. Ahmadzia *et al.* report an overall increase of 1.7% in cases of PPH cause by uterine atony in the period 2001-2002 to 2011-2012. When categorised, there is a 10.6% reduction in uterine atony cases with vaginal birth but an increase of 61.1% when delivered through caesarean section. They also report an increase in caesarean sections from 25.8% to 33.3% in this timeframe.[9] Thurn *et al.* reports a 30% increase in massive transfusion rates postpartum to 5.3 per 10,000 deliveries. Previous caesarean section (OR 4, 95% CI [3.1-6.0]) alone and abnormal placentation (OR 41, 95% CI [29.3-58.1]) were highly associated with this rise in massive transfusion rate.[10] Other studies also report this same association.[11-13] Even though increased caesarean rate and therefore placenta accreta spectrum (PAS) seems a plausible explanation for the rising incidence, there are reports of a rising trend of PPH after vaginal births. Flood *et al.* reports an increase of 9.7% to 15.3% of postpartum haemorrhage between 2003 to 2013 when PPH is defined as ≥ 500 mL blood loss.[6] Ford *et al.* reports an increase from 7.0% to 9.5% in PPH in vaginal births.[14] This same study also reports a decrease in maternal morbidity despite the rise in PPH in vaginal births with an adjusted odd ratio of 0.64 (95% ci [0.47-0.87], p 0.05) in 2010 compared to 2003.[14] This difference was not seen in caesarean sections in this cohort. Evidently, (fluid) resuscitation policy remains a relevant topic in modern day PPH care.

We found no disadvantages of a restrictive fluid resuscitation policy in comparison to a liberal resuscitation policy in patients with a PPH ≤ 1500 mL on progression to > 1000 mL blood loss, need for blood transfusion, and on haemostatic parameters. Retrospective research by two other research groups indicates a negative effect of liberal resuscitation policy in severe PPH. These results, in addition to our own RCT, make a restrictive fluid resuscitation policy the treatment of choice in patients with a PPH ≤ 1500 mL.

The national NVOG protocol on haemorrhagia postpartum can be additionally supported with this data and international guidelines can use our data in their guidelines.

Thromboelastometry is useful to individualise treatment in patients with PPH. The use of point-of-care assays such as thromboelastometry fits within patient-centred-care policies.

IMPLICATIONS FOR FUTURE RESEARCH

Questions remaining are the effect of fluid resuscitation and the optimal timing for thromboelastometry in daily practice in severe postpartum haemorrhage.

Even though we did not show a statistically significant advantage of a restrictive fluid policy, we also did not show a disadvantage in patients with PPH ≤ 1500 mL. Therefore, we conclude that another RCT with a bigger patient population set within the same regimen would be unnecessary research for patients to participate in. We would suggest investing in implementation of the restrictive approach in patients with PPH.

In regard to the optimal timing for thromboelastometry in daily practice, a prospective analysis is preferred.

Further research as to why postpartum haemorrhage is rising deserves attention. For now, increasing rates of caesarean section and accompanying complications such as placental adherence problems seems one of the main factors. The rising incidence of PPH in vaginal births combined with a lower morbidity might suggest fewer severe haemorrhages occur in vaginal delivery, different management or better recording. This requires further, separate, attention from PPH after caesarean with or without its relation to placental adherence pathology.

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8

Impact

ONDERZOEK

Bloedverlies na de bevalling is wereldwijd nog altijd een van de grootste oorzaken van maternale morbiditeit en mortaliteit. In Nederland is de incidentie gestegen van 4.1% in 2000 naar 6.4% in 2013.[1] De laatste jaren is deze stijgende trend gestabiliseerd naar een incidentie tussen de 6.1 – 6.4%.[2] In Nederland wordt ruim bloedverlies na de bevalling, een fluxus postpartum, gedefinieerd als bloedverlies van 1000 mL of meer. De World Health Organization (WHO) definieert een fluxus postpartum als bloedverlies in de eerste 24 uur na de bevalling van 500 mL of meer.[3] Er is geen eenduidig beleid omtrent de vullingsstrategie bij vrouwen die ruim bloedverlies hebben na hun bevalling. Er zijn verschillende richtlijnen en adviezen met betrekking tot vullingsstrategie na ernstig bloedverlies in omloop, helaas zijn deze adviezen niet specifiek gericht op en getoetst bij de zwangere en bevallende vrouw (zie hoofdstukken 2 en 3).

Uit dierstudies, militaire onderzoeken en trauma onderzoeken lijkt er mogelijk een voordeel te bestaan met betrekking tot overleving en andere complicaties bij een restrictief vullingsbeleid, waarbij (ongeveer) het verloren bloedvolume gesuppleerd wordt maar niet meer (zie hoofdstuk 3). Er zijn ook methodes die zich richten op een gemiddelde arteriële druk (de zgn. *mean arterial pressure,* MAP). Bij aanvang van het onderzoek in dit proefschrift was er geen onderzoek beschikbaar over een vullingsbeleid met heldere vloeistoffen bij ruim bloedverlies na de bevalling. De zwangere vrouw heeft een uniek adaptatie systeem (zie hoofdstuk 1) wat maakt dat onderzoek op andere populaties niet direct op haar toepasbaar is.

Het algemene doel van dit proefschrift was om de wetenschappelijke basis voor behandeling bij bloedverlies postpartum te versterken. Hiervoor hebben wij gekeken naar het effect van ruime versus restrictieve vulling met heldere vloeistoffen bij ruim bloedverlies postpartum met betrekking tot de progressie naar een ernstige bloeding postpartum. Daarnaast evalueerden we het effect van deze vullingsstrategieën op klassieke en visco-elastische stollingsparameters

RELEVANTIE

Om voor de barende vrouw een vullingsstrategie te kunnen adviseren was gerandomiseerd onderzoek nodig. In onze gerandomiseerde studie is onderzocht of een restrictief vullingsbeleid met heldere vloeistoffen minder progressie gaf naar een ernstigere bloeding na de bevalling in vergelijking met een ruim vullingsbeleid (zie hoofdstuk 4). De veranderde hemostatische parameters in de zwangerschap zijn erop

gericht om ruim bloedverlies te voorkomen, hierdoor is het mogelijk dat vulling, door verdunning, een negatief effect zou kunnen hebben op de stollingspotentie. Vandaar dat we het effect van deze vullingsstrategieën op de hemostase hebben bekeken. Ons onderzoek laat geen verschil zien in progressie naar ernstig bloedverlies (meer dan 1000 mL), de hoeveelheid bloedtransfusies of in de hemostatische parameters tussen beide onderzoeksgroepen (zie hoofdstukken 4 en 6).

Uit ons onderzoek blijkt dat beide vullingsstrategieën gelijkwaardig zijn indien het bloedverlies minder dan 1500 mL betreft. In de restrictieve arm zijn 51 van de 130 (39.2%) vrouwen gecontinueerd naar meer dan 1000 mL bloedverlies tegenover 61 van de 119 (51.3%) van de vrouwen in de ruime vullingsgroep. Het gemiddelde verschil in risico is hierbij -12.0% in het voordeel van het restrictieve vullingsbeleid met een 95%-betrouwbaarheidsinterval van -24.3% tot 0.3%. Een restrictiever beleid is dus niet slechter dan een ruime vullingsstrategie. Ondanks het statistisch niet-significante verschil, kan beargumenteerd worden dat een restrictief beleid mogelijk beter is dan een ruimer vullingsbeleid gezien de reikwijdte van dit interval van -24.3% tot 0.3% [4].

Er zijn aanwijzingen dat in een later stadium, bij ruimer bloedverlies, een ruime vulling tot slechtere uitkomsten leidt. In retrospectief onderzoek werd toediening van grotere volumes heldere vloeistof geassocieerd met verslechtering van stollingswaarden. Bij toediening van meer dan 4 L heldere vloeistof werd een grotere kans op ernstige uitkomsten voor de moeder gevonden zoals overlijden, embolisatie behandeling of baarmoederverwijdering.[5, 6]

Dat een restrictiever vullingsbeleid met heldere vloeistoffen geen bewezen nadelen heeft in een vroeg stadium kan voordelig zijn in een later stadium. Er is nog geen prospectief onderzoek verricht naar het effect van vullingsbeleid met heldere vloeistoffen bij een ernstige bloeding postpartum (> 1500 mL). Idealiter zou een gerandomiseerde studie wenselijk zijn bij de groep vrouwen met meer dan 1500 mL bloedverlies om deze retrospectieve bevindingen te bevestigen. Echter is dit onderzoek lastig haalbaar in verband met het weinig voorkomen van deze ruime bloedingen. Postpartum bloedingen van meer dan 1500 mL hebben een incidentie tussen de 1.4% en 3.9%.[7, 8] Hiermee is de hoeveelheid potentiële proefpersonen te informeren versus de hoeveelheid daadwerkelijke inclusies in deze studie sterk uit balans. Er zullen veel meer vrouwen om toestemming gevraagd moeten worden dan er daadwerkelijk kunnen deelnemen vanwege de onvoorspelbaarheid van het optreden van een bloeding. Dit resulteerde bij ons onderzoek in vele malen meer “informed consent” formulieren dan daadwerkelijke inclusies. Pas op het moment van de daadwerkelijke bloeding “informed consent” vragen zou in strijd zijn met het

verdrag van Helsinki omdat patiënte geen redelijke bedenktijd krijgt. Gezien een bloeding van meer dan 1500 mL veel minder vaak voorkomt dan een bloeding van 500 mL lijkt dit een onhaalbaar onderzoek te zijn. Naast deze praktische bezwaren komt eveneens de vraag naar voren wanneer het juiste moment van randomisatie is, en hoe men rekening houdt met het vullingsbeleid dat werd gehanteerd voordat het bloedverlies 1500 mL overschreed. Deze vraagstukken zullen een nieuw onderzoek bemoeilijken.

Buiten de logistieke uitdagingen kan men zich afvragen of het ethisch verantwoord is om de groep vrouwen met een bloeding postpartum te behandelen met een ruim vullingsbeleid na de resultaten van ons onderzoek in combinatie met de retrospectieve onderzoeken van Gillissen en Henriquez.[5, 6] Er kan overwogen worden om een prospectief cohort onderzoek op te zetten, maar een gerandomiseerd onderzoek naar het vullingsbeleid met heldere vloeistoffen bij vrouwen met meer dan 1500 mL bloedverlies postpartum lijkt vooralsnog niet bij te dragen aan bestaande bevindingen.

DOELGROEP

De doelgroep van dit proefschrift is breed: de nationale beroepsvereniging Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) en de internationale verenigingen die richtlijnen ontwikkelen waarin de behandeling van ruim bloedverlies na de bevalling wordt omschreven als zowel als de specialisten die zorg leveren rondom de bevalling zoals gynaecologen, verloskundigen en anesthesisten. De uiteindelijke doelgroep betreft nog altijd de barende vrouw zelf. Immers voor de barende vrouw is het van belang dat er evidence-based protocollen bestaan die haar behandeling ten goede komen. De (inter)nationale richtlijn kan nu met gerandomiseerd onderzoek gespecificeerd op de zwangere vrouw worden ondersteund.

ACTIVITEIT

De richtlijn van de NVOG was reeds aangepast naar aanleiding van literatuuronderzoek verricht in het kader van onze onderzoeksvragen. Deze richtlijn kan nu duidelijker onderbouwd worden voor vrouwen met bloedverlies tot 1500 mL, waarbij het onwaarschijnlijk is dat bij ruimer bloedverlies ruim vullen wel zinnig is. Het nationale protocol vormt de basis voor meerdere lokale protocollen. Daarbuiten zijn de resultaten van ons gerandomiseerd onderzoek ook in het vakblad Nederlands Tijdschrift van Obstetrie en Gynaecologie (NTOG) gepubliceerd.[9]

Ons onderzoek is internationaal gepubliceerd in diverse internationale journals die o.a. bereikbaar zijn via PubMed, Web of Science en EMBASE. De hoofdresultaten zijn gepubliceerd als "open access" artikelen waardoor iedereen de resultaten kan inzien zonder betaling. Richtlijnontwikkelaars kunnen onze data bereiken via deze bekende zoekkanalen en meenemen in de onderbouwing van de richtlijnen.

De echte uitdaging zal zitten in de daadwerkelijke implementatie van deze resultaten op de dagelijkse werkvloer zowel binnen als buiten Nederland. Het model van Wensing en Grol beschrijft 5 fasen die een individu, groep of organisatie ondergaan om tot implementatie en integratie van een nieuwe werkwijze te komen: oriëntatie, inzicht, acceptatie, verandering en behoud.[10] Voor diverse lagen zijn verschillende fases al doorlopen. Binnen de gynaecologie is de oriëntatie en een deel van de inzichtfase bewerkstelligd middels dit proefschrift, de publicaties die vrij beschikbaar zijn en het aanpassen van de nationale richtlijn. De acceptatiefase, waarin de doelgroep gemotiveerd wordt om tot verandering over te gaan, is nog incompleet. Doordat het advies is opgenomen in de nationale richtlijn van de NVOG zal binnen de vakgroepen gynaecologie in Nederland de urgentie moeten ontstaan om lokale protocollen aan te passen naar deze adviezen. Binnen het MUMC+, vakgroep obstetrie, zitten we in de veranderfase waarbij een start is gemaakt met het uitvoeren van deze adviezen.

Naast implementatie binnen onze eigen vakgroep zal de implementatie buiten de eigen, maar nauw aanpalende vakgroepen, moeten geschieden. Specifiek voor de Gynaecologie en Obstetrie is dit de vakgroep Anesthesie en de ambulancedienst. Om de oriëntatiefase op te starten binnen deze vakgroepen zou gebruik gemaakt kunnen worden van refereeravonden waarbij de onderzoeken van dit proefschrift worden gepresenteerd. Gezien de strekking van onze resultaten in lijn ligt met de huidige adviezen vanuit de Europese richtlijn voor massale bloedingen gedateerd uit 2019 en die uit 2016, kan verwacht worden dat de oriëntatiefase en inzichtfase vlot kunnen verlopen.[11, 12] In deze richtlijn wordt geadviseerd een restrictief vullingsbeleid te handhaven om de streefbloeddruk te bereiken, zo nodig in combinatie met vasopressor medicatie. Deze streefbloeddrukken zijn 80-90 mmHg systolisch streefbloeddruk te halen. In deze oriëntatiefase kunnen de beginselen van een discipline overstijgend protocol ontstaan met betrekking tot de bloeding postpartum.

Concluderend was er aan de start van dit proefschrift weinig tot geen onderzoek naar vullingsstrategie met heldere vloeistoffen bij de barende met ruim bloedverlies na de bevalling. Uit onderzoek bij andere doelgroepen leek er een voordeel te zijn met betrekking tot een restrictiever vullingsbeleid. Uit ons gerandomiseerde onderzoek blijkt dat beide strategieën gelijkwaardig zijn met betrekking tot progressie naar meer dan

1000 mL bloedverlies en het effect op klassieke en visco-elastische stollingsparameters bij vrouwen met bloedverlies postpartum tot 1500 mL. Gecombineerd met ander onderzoek dat in de tussentijd gepubliceerd is er momenteel geen reden om meer bij te vullen dan verloren in bloedvolume bij vrouwen met een bloeding postpartum tot 1500 mL.

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9

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Dit proefschrift vergelijkt een ruim vullingsbeleid met een restrictief vullingsbeleid tijdens een fluxus postpartum.

Hoofdstuk 1: Algemene inleiding

Wereldwijd is ruim bloedverlies na de bevallen, een fluxus postpartum, een van de grootste oorzaken van maternale mortaliteit en morbiditeit. De incidentie stijgt in zowel Nederland als daarbuiten. De incidentie in Nederland was 6.2% in 2022. De grootste oorzaak is en blijft atonie waarbij de baarmoeder niet goed samentrekt na de bevalling. Diverse risicofactoren vergroten de kans op een fluxus postpartum. Ondanks een toename van deze risicofactoren, zoals maternale leeftijd, inleiding van de bevalling, meerlingzwangerschappen etc., blijft na correctie voor deze risicofactoren de incidentie van fluxus postpartum toenemen. Derhalve is het van belang om ook naar andere, mogelijk, bijdragende factoren te kijken zoals de behandeling bij een fluxus postpartum.

De behandeling van een fluxus postpartum bestaat uit een combinatie van medicatie (uterotonica), chirurgie, ondersteuning en correctie van de stolling, en volume resuscitatie met heldere vloeistoffen en bloedproducten. Volume resuscitatie met kristalloïden, colloïden en bloedproducten hebben allemaal eigen voor- en nadelen. De behandeling is gericht op het oplossen van de onderliggende oorzaak van het bloedverlies en ondertussen de barende hemodynamisch stabiel te houden. Bij de start van deze thesis was er weinig tot geen onderzoek binnen de verloskunde beschreven naar volume resuscitatie met heldere vloeistoffen, het effect op progressie van de fluxus en het effect hiervan op de coagulatie. De toen geldende richtlijnen adviseerde een ruim vullingsbeleid met heldere vloeistoffen met het dubbele als het verloren bloed. In andere vakgebieden zijn meer onderzoeken te vinden waaruit sommige studies een mogelijk voordeel lieten zien voor een meer restrictief vullingsbeleid. Andere studies laten geen grote verschillen zien. Deze studies zijn meestal underpowered en uitgevoerd bij een niet zwangere patiënt.

De zwangere vrouw ondergaat cardiovasculaire en hemostatische veranderingen door waardoor resultaten verkregen bij andere studiegroepen niet een-op-een te extrapoleren zijn.

In hoofdstuk 1 wordt verder het gebruik van de tromboelastometrie middels ROTEM® uiteengezet. Het grootste voordeel van deze methode is de snelheid waarmee resultaten kunnen worden verkregen.

Hoofstuk 1 wordt afgesloten met een uiteenzetting van de thesis doelen met het generieke doel om bij te dragen aan 'evidence based care' bij een fluxus postpartum.

Hoofdstuk 2: Liberale of restrictieve vulling tijdens electieve chirurgie
In hoofdstuk 2 is een systematische review met meta-analyse uitgevoerd van 12 gerandomiseerde studies die een restrictief vullingsbeleid middels kristalloïden en colloïden vergeleek met een ruim vullingsbeleid tijdens electieve chirurgie. De twaalf studies bevatte 1397 patiënten (693 in de restrictieve groep, 704 in de liberale groep). De liberale groep ontving meer vulling dat de restrictieve groep (mean 4048 mL, range 2928 - 5775 mL versus mean 2019 mL, range 997.5 - 3517 mL resp.) Meta-analyse liet een voordeel zien voor de restrictieve groep in de hoeveelheid patiënten met een complicatie in de eerste 30 dagen na chirurgie (RR 0.65, CI 95%: 0.55-0.78). We zagen een lagere totale complicatieratio (RR 0.57, CI 95%:0.52-0.64), minder infecties (RR 0.62, CI 95%: 0.48-0.79) en minder bloedtransfusies (RR 0.81, CI 95% 0.66-0.99) in de restrictieve groep. De postoperatieve nabloedingen verschilde niet in de groepen RR 0.76 (CI 95%: 0.28-2.06). Derhalve een restrictief vullingsbeleid tijdens electieve chirurgie zorgt voor een 35% reductie in complicaties en een verminderde noodzaak in bloedtransfusies.

Hoofdstuk 3: Restrictief versus ruime vulling en de invloed op bloedverlies en hemostase bij een fluxus postpartum: een open-label randomised controlled trial (studieprotocol)
Hoofdstuk 3 beschrijft het studieprotocol dat gebruikt is voor de opzet van de REFILL studie en deze thesis. Het geeft achtergrondinformatie waarom de uitvoer van deze studie juist zo belangrijk is voor de dagelijkse praktijk. Fluxus postpartum is een van de grootste oorzaak van maternale mortaliteit en morbiditeit en komt steeds vaker voor in ontwikkelde landen ondanks het bestaan van richtlijnen en trainingen. Ook bij het corrigeren van risicofactoren blijft een stijging in incidentie waarneembaar. De huidige richtlijnen geven als advies een ruim vullingsbeleid, tot wel 2x zoveel vocht teruggeven als verloren. Dit advies is niet gestoeld op “evidence based medicine” en kan potentieel schade berokkenen aan de patiënt.

Het doel van de REFILL studie is om te bepalen bij vrouwen met een milde fluxus postpartum (bloedverlies 500 - 750 mL) of bij een restrictief vullingsbeleid in vergelijking met de standaardbehandeling er minder progressie is naar een ernstige fluxus postpartum (bloedverlies > 1000 mL). Wij denken dat een restrictief vullingsbeleid leidt tot verminderde progressie naar een ernstige fluxus postpartum en daarmee ook een vermindering van morbiditeit.

Wij hebben een powerberekening verricht waaruit kwam dat 250 vrouwen geïncludeerd moeten worden. Hierbij is rekening gehouden met loss to follow-up. De primaire en secundaire uitkomstmaten zijn hieronder benoemd.

Primaire uitkomstmaat
De primaire uitkomstmaat is om te bepalen of vrouwen met een milde fluxus postpartum (bloedverlies 500 – 750 mL) of bij een restrictief vullingsbeleid in vergelijking met de standaardbehandeling minder progressie is naar een ernstige fluxus postpartum hebben (bloedverlies > 1000 mL).

Secundaire uitkomstmaten
Secundaire uitkomstmaten zijn: verschil in Hb (mmol/L) 12-18 uur postpartum, verschil in coagulopathie gedefinieerd als afwijkende laboratorium testen (Hb < 5.0 mmol/L, trombocyten < 50x10^9, fibrinogeen < 1g/L, en APTT en PT > 1.5x normaalwaarde). Ernstige morbiditeit werd gemeld: intensive care opname, > 4 packed cells, embolisatie van de uteriene vaten en/of hysterectomie.

Hoofdstuk 4: Restrictief versus ruime vulling en de invloed op bloedverlies en hemostase bij een milde fluxus postpartum: een open-label randomised controlled trial.
Hoofdstuk 4 beschrijft de hoofdresultaten die zijn voortgekomen uit de in hoofdstuk 3 beschreven studie. Van augustus 2014 tot september 2019 zijn 5190 patiënten beoordeeld voor geschiktheid van de studie waarvan 1622 gevraagd zijn voor deelname indien er meer dan 500 mL bloedverlies zou optreden postpartum. Totaal zijn er 252 patiënten daadwerkelijk gerandomiseerd. 130 in de restrictieve groep en 122 in de liberale groep. 3 patiënten zijn voortijdig gestopt met de studie in verband met pre-eclampsie ontwikkeling en zijn niet meegenomen in de analyse. Uiteindelijk is data van 130 patiënten in de restrictieve groep en 119 patiënten in de liberale groep geanalyseerd. Er kwamen geen significante verschillen tussen de groepen naar voren in de primaire en de secundaire uitkomstmaten. Voor de primaire uitkomstmaat, progressie naar meer dan 1000 mL bloedverlies postpartum, waren er in de restrictieve groep 51/130 (39,2%) patiënten versus 61/119 (51,3%) patiënten in de liberale groep, p = 0.057, verschil -12.0% [95%-CI -24.3% to 0.3%].

Een meer restrictief vullingsbeleid is niet bewezen superieur aan een liberaal vullingsbeleid maar gaf niet meer behoefte aan bloedtransfusie, veranderde niet evident de hematologische uitkomsten, of veroorzaakte niet meer ernstige uitkomsten. Daarom kan een meer restrictief vullingsbeleid als alternatieve behandeling ingezet worden bij een milde fluxus postpartum.

Hoofdstuk 5: Thromboelastometrie in de dagelijkse praktijk: wanneer is een afwijkend resultaat te verwachten? Een retrospectief klinische observationele studie.
Hoofdstuk 5 onderzoekt de thromboelastometry in de dagelijkse obstetrische praktijk. Wij hebben een retrospectief klinisch observationele studie verricht waarin alle ROTEM® waarden zijn verzameld van vrouwen met een fluxus postpartum in Maastricht Universitair Medisch Centrum tussen 2014 en 2016. Data van 139 vrouwen zijn verzameld uit hun klinisch status. Patiënten werden verdeeld in drie groepen: minder dan 1000 mL bloedverlies, tussen 1000 en 1999 mL bloedverlies en 2000 mL of meer bloedverlies. De kansen op een afwijkend resultaat in de stollingstijd (CT) van de INTEM en EXTEM en de FIBTEM A10 waardes zijn vergeleken tussen de drie groepen. De resultaten laten zien dat de kans op een afwijkende waarde toeneemt met het hoeveelheid bloedverlies. Dit is in lijn met eerder gepubliceerde data, echter onze resultaten waren niet alleen afwijkend in de FIBTEM arm en meer dan 80% van de vrouwen in deze studie hadden normale waarden.

Hoofdstuk 6: Restrictieve versus ruime vullingsstrategie bij milde fluxus postpartum en de invloed op thromboelastometrie (ROTEM®) en hemostatische parameters.
Hoofdstuk 6 beschrijft een subgroep analyse vanuit hoofdstuk 4.Bij vrouwen die bevielen in het Maastricht Universitair Medisch Centrum (MUMC+) en het Zuyderland Medisch Centrum werd ook een thromboelastometrie (ROTEM®) meting verricht naast de reguliere bloedafnames met betrekking tot de REFILL studie zoals beschreven in hoofdstuk 3 en 4. Er zijn thromboelastometrie (ROTEM®) analyses verricht in totaal 72 vrouwen, 36 in de restrictieve vullingsgroep en 36 in de ruime vullingsgroep direct na randomisatie en 45-60minuten na randomisatie. Er kon geen invloed van vullingsstrategie op thromboelastometrie (ROTEM®) waarden worden aangetoond. Daarna is de gehele studiepopulatie (n = 252) geanalyseerd. Er kon geen invloed van gerandomiseerde vullingsstrategie worden aangetoond op fibrinogeen waarden, Activated Partial Thromboplastin Time (APTT) en Partial Thromboplastin Time (PT). Derhalve in vrouwen met een postpartum bloeding van 1500 mL of minder is er geen invloed van vullingsstrategie op hemostatische parameters aangetoond.

Hoofdstuk 7: Engelse samenvatting en algemene discussie
Hoofdstuk 7 geeft de samenvatting en tevens discussie van dit proefschrift weer. Focus van dit proefschrift was om de bestaande behandelingen te evalueren met betrekking tot resuscitatie met heldere vloeistoffen tijdens een bloeding postpartum. Binnen het obstetrie deelgebied waren de adviezen vooral gebaseerd op data buiten het obstetrie gebied. Data derhalve niet specifiek gebaseerd op de zwangere en barende vrouw. In hoofdstuk 7 wordt een samenvatting van alle hoofdstukken beschreven zoals hierboven in het Nederlands weergegeven.

De resultaten van ons gerandomiseerd onderzoek tonen geen significant verschil tussen een restrictief vullingsbeleid met heldere vloeistoffen versus een ruim vullingsbeleid in milde fluxus postpartum of een effect hiervan op klassieke en visco-elastische hemostatische parameters. Er is geen nadeel van een restrictievere benadering. Additioneel onderzoek gepubliceerd door Gillisen *et al.* en Henriquez *et al.* in 2018 en 2018 laat retrospectief een nadeel zien van een ruim vullingsbeleid bij ernstige fluxus postpartum en op hemostatische parameters. Samengenomen dat in andere deelgebieden er een voordeel lijkt te zijn van een restrictievere methode in combinatie met onze resultaten uit het gerandomiseerde onderzoek en rekening houdend met de resultaten van het retrospectieve onderzoek van Gillisen *et al.* en Henriquez *et al.* concluderen we dat resuscitatie met heldere vloeistoffen in een milde fluxus postpartum restrictief dient te gebeuren. Dat wil zeggen: vervangen van het verloren bloedvolume met gelijke hoeveelheid volume in kristalloïden.

In hoofdstuk 7 worden verder de moeilijkheden besproken die samenhangen met gerandomiseerd onderzoek in deze acute setting. Daarbij worden de implicaties voor de dagelijkse praktijk en toekomstig onderzoek besproken.


D

Dankwoord

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DANKWOORD

Het is klaar! Wat begon als een kort informatief gesprek over een geheel ander onderwerp op de oude stafgang van het MUMC+, koud drie maanden na start van de opleiding en een verhuizing van 220 km, is uitgemond tot een echt proefschrift. Ik ben trots dat dit bereikt is, ik had dit niet alleen gekund en wil daarom iedereen bedanken die heeft bijgedragen aan deze reis.

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List of publications

REFILL STUDY

1. Schol PB, Terink IM, Lance MD, Scheepers HC. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. *Journal of clinical anesthesia* 2016; **35**: 26-39
2. de Lange N, Schol P, Lance M, et al. Restrictive Versus Massive Fluid Resuscitation Strategy (REFILL study), influence on blood loss and hemostatic parameters in obstetric hemorrhage: study protocol for a randomized controlled trial. *Trials* 2018; **19**: 166
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4. Schol PBB, de Lange NM, Smits LJM, Henskens YMC, Scheepers HCJ. Thromboelastometry in daily obstetric practice: At what amount of blood loss do we find abnormal results? A retrospective clinical observational study. *Thrombosis research* 2021; **207**: 140-2

OTHER PUBLICATIONS

1. Schol PB, De Waard J, Van Praag MC, Noordhoek Hegt V, Van Der Weiden RM. Vaginal sarcoidosis. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology* 2013; **33**: 426
2. Schol PB, Guzel C, Steegers EA, de Krijger RR, Luider TM. Trophoblast calcyclin is elevated in placental tissue from patients with early pre-eclampsia. *Pregnancy hypertension* 2014; **4**: 7-10
3. Toonen D, Schol, P.B.B., Smeets, N.A.C. [A woman with micturition problems]. *Nederlands tijdschrift voor geneeskunde* 2021; **165**:D5944


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Curriculum vitae

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CURRICULUM VITAE

Pim Schol is geboren in Rotterdam op 13 oktober 1987. Zij behaalde haar tweetalig VWO diploma aan het Wolfert van Borselen te Rotterdam in 2005 waarna zij geneeskunde studeerde aan de Universiteit Leiden. Na het behalen van haar arts examen in 2012 kon zij direct aan de slag als ANIOS in het Sint Franciscus Gasthuis in Rotterdam. In 2014 is zij gestart met de opleiding tot gynaecoloog in het toenmalige Atrium in Heerlen. Kort na de start van de opleiding is het promotietraject gestart onder leiding van Liesbeth Scheepers. Het academische deel van de opleiding is gevolgd in het Maastricht UMC+. Na het basiscurriculum van de opleiding heeft Pim een differentiatie minimaal invasieve chirurgie in het Zuyderland Medisch Centrum gevolgd en een differentiatie Obstetrie in het Maastricht UMC+ gevolgd. Per september 2020 heeft zij de opleiding tot gynaecoloog afgerond waarna zij is gaan werken als chef-de-clinique in het Zuyderland Medisch Centrum. Per september 2021 is zij toegetreden tot de staf van de Obstetrie in het Maastricht UMC+ en werkt zij hier met veel plezier. Pim woont in Maastricht samen met Tom en hun kinderen Philip en Bobbi.