Postpartum hemorrhage: from insight to action

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CHAPTER 5

COMPARISON OF OUTCOME BETWEEN INTRAUTERINE BALLOON TAMPONADE AND UTERINE ARTERY EMBOLIZATION IN THE MANAGEMENT OF PERSISTENT POSTPARTUM HEMORRHAGE: A PROPENSITY SCORE-MATCHED COHORT STUDY

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ABSTRACT

Introduction

To compare the outcomes of women who were initially managed by intrauterine balloon tamponade or uterine artery embolization because of persistent postpartum hemorrhage demanding an immediate intervention to control bleeding.

Material and methods

Propensity score matched cohort study including women who had intrauterine balloon tamponade or uterine artery embolization as initial management strategy to control persistent postpartum hemorrhage, i.e. refractory to first-line therapy combined with at least one uterotonic agent. The primary outcome measure was a composite of peripartum hysterectomy and/or maternal mortality. Secondary outcomes measures were total volume of blood loss and total number of packed red blood cells transfused.

Results

Our 1:1 propensity score matched cohort comprised of 50 women who had intrauterine balloon tamponade and 50 women who underwent uterine artery embolization at a blood loss between 1000 and 7000mL. There was no statistically significant difference in the hysterectomy risk between both groups (N=6 in each group, OR 1.00, 95% CI; 0.30 to 3.34), nor in total volume of blood loss (median 4500mL [IQR; 3600 to 5400] for balloon versus 4000mL [IQR; 3250 to 5000] for embolization, p=0.382), nor in total units of packed red blood cells transfused (median 7 [IQR; 5 to 10] for balloon versus 6 [IQR; 4 to 9] for embolization, p=0.319). Fifteen women (30%) who were initially managed by an intrauterine balloon still underwent uterine artery embolization, of whom one had an embolization-related thrombo-embolic event. Maternal mortality occurred in neither of the intervention groups.

Conclusions

No difference in the risk of hysterectomy and/or maternal death was observed between women who had intrauterine balloon tamponade and women who underwent uterine artery embolization as an initial management for persistent postpartum hemorrhage. Although this study was underpowered to demonstrate equivalence, our study design provides a rational framework for future research in which intrauterine balloon tamponade may prove to be a suitable intervention of first choice in the management of persistent postpartum hemorrhage.

INTRODUCTION

Postpartum hemorrhage remains the leading cause of maternal mortality around the world.[1] There is an international call for improving maternal safety and the evaluation of obstetric care is crucial to answer this call and reduce maternal deaths, which are often preventable.[2] Peripartum hysterectomy can be performed as a life-saving procedure of last resort, but leads to infertility, accompanied by substantial morbidity and psychosocial sequelae.[3-5] Various invasive and less invasive management strategies were developed to reduce the need for hysterectomy, including intrauterine balloon tamponade, uterine compression sutures, and devascularisation of the uterine artery by surgical ligation or radiological embolization.[6]

Uterine artery embolization may be used to manage persistent postpartum hemorrhage that demands immediate intervention before proceeding to hysterectomy, but it is considered as a relatively costly and invasive procedure that is prone to a number of complications (e.g. post-embolization syndrome, thrombo-embolic events, or uterine necrosis).[7-10] On the other hand, intrauterine balloon tamponade has emerged as an inexpensive and less invasive option to control ongoing bleeding.[11-13] Insertion of an intrauterine balloon for the purpose of tamponade during postpartum hemorrhage could potentially obviate the need for uterine artery embolization, and reduce health care costs. However, these interventions have never been compared in terms of their effectiveness of preventing severe maternal outcome (i.e. maternal death or a near miss averted by a peripartum hysterectomy), and thus uncertainty persists as to whether intrauterine balloon tamponade is an effective alternative to uterine artery embolization when both interventions are considered as possible options during the course of postpartum hemorrhage.

Aim of this study was to compare severe maternal outcome in women who received intrauterine balloon tamponade with women who had uterine artery embolization as initial management for persistent postpartum hemorrhage in whom immediate intervention was deemed necessary.

MATERIALS AND METHODS

Given the fact that intrauterine tamponade with a balloon-like device is less invasive and much easier to perform than uterine artery embolization, it is possible that intrauterine balloon tamponade is more often used in women with less severe bleeding. Women receiving intrauterine balloon tamponade may also differ in various ways from women undergoing uterine artery embolization. For these reasons, we used propensity score matching to correct for any confounding by indication. Using this technique, we constructed a cohort of women who differed with respect to the management strategy applied, but were similar with respect to all other clinically relevant characteristics that could have influenced the clinician's decision to apply either one of the interventions during persistent postpartum hemorrhage.[14]

Data source

This study used data from the *Transfusion strategies in women during Major Obstetric Haemorrhage* study (TeMpOH-1). The TeMpOH-1 study was a nationwide retrospective cohort study in 61 hospitals in the Netherlands (71% of all hospitals in the country) in which data from medical files of pregnant women of at least 18 years old were included. These women had received at least four units of packed red blood cells or any transfusion of fresh frozen plasma and/or platelets in addition to packed red blood cells because of obstetric hemorrhage (≥1000mL blood loss during pregnancy or the first 24 hours following birth) between January 1st, 2011 and January 1st, 2013. Eligible women were identified by cross-referencing data from hospitals' blood transfusion services with the local birth registers in participating hospitals. Trained medical students and research nurses obtained available data from medical records present in maternity units, operating theatres, and intensive care units.

Cohort selection

From the TeMpOH-1 database, we identified all women who were initially managed by intrauterine balloon tamponade or uterine artery embolization during persistent postpartum hemorrhage. Persistent postpartum hemorrhage was defined as ongoing hemorrhage within the first 24 hours following birth, refractory to first-line therapy (previously defined per primary cause of hemorrhage, Table S1)[15] combined with the administration of at least one uterotonic agent (including oxytocin [prophylactic use of oxytocin following childbirth excluded], ergometrine, misoprostol, or sulprostone). By using this definition of persistent postpartum hemorrhage, we avoided a definition solely based on mere estimation of blood loss and ensured that women included in

this study received minimally necessary care per cause of hemorrhage prior to use of intrauterine balloon tamponade or uterine artery embolization. However, since no uterine artery embolizations were performed below 1000mL of blood loss and no intrauterine balloons were inserted above 7000mL of blood loss (Figure S1), we restricted our analyses to women who had intrauterine balloon tamponade or uterine artery embolization between these limits of blood loss. Furthermore, although the Bakri® balloon (Cook Medical, Bloomington, USA) is the type of intrauterine balloon device mostly used in the Netherlands, the TeMpoH-1 study did not specifically register which type of device was inserted. Therefore, this study defined intrauterine balloon tamponade as insertion of any type of balloon catheter into the uterine cavity for the purpose of tamponade. Women were classified depending on the intervention (i.e. balloon or embolization) that was first applied and they were considered to remain in that intervention group until the end of hemorrhage or occurrence of the primary outcome.

Outcome measures

The World Health Organisation developed the Maternal Near Miss (MNM) tool to enable uniform identification of those women who nearly died but survived a complication during pregnancy, childbirth, or within 42 days of termination of pregnancy.[16] In this approach, women who underwent hysterectomy due to hemorrhage are considered as MNM. The reason to perform uterine balloon tamponade or uterine artery embolization is to control intractable bleeding, and avert severe maternal outcome (i.e. maternal death or MNM). Hence, we used a composite of maternal death or MNM averted by hysterectomy as the *primary outcome measure*. If this primary outcome did not occur, end of bleeding was defined as the time of the last estimated blood loss measurement. *Secondary outcome measures* were total estimated volume of blood loss and total number of packed red blood cells transfused.

Statistical analyses

The propensity score, representing the probability of receiving intrauterine balloon tamponade during the course of persistent postpartum hemorrhage, was estimated by a logistic regression model with intrauterine balloon tamponade inserted between an estimated blood loss of 1000 to 7000mL as the dependent variable. Characteristics considered as potential confounders for the association between use of intrauterine balloon tamponade or use of uterine artery embolization, or characteristics considered to be risk factors for the occurrence of the primary outcome measure alone, were included as covariates in the propensity score model.[17]

Characteristics included as covariates that were available at the moment the clinician decided to use an intrauterine balloon tamponade or to perform uterine artery embolization were: maternal age, gestational age, parity (nulliparity or multiparity), preeclampsia, multiple pregnancy, prior cesarean birth, mode of birth (vaginal birth or cesarean section), cause of hemorrhage (categorized as uterine atony, retained placenta, abnormally invasive placenta, and other causes [composite of placenta previa, placental abruption, and uterine rupture due to small numbers]), presence of coagulopathy (defined as a fibrinogen level ≤2 g/L during bleeding), symptoms of shock (defined as at least one measurement of a systolic blood pressure ≤90mmHg and/or heart rate ≥120 beats per minute during bleeding), volume of blood loss at time of intervention (measured by weighing gauzes or other soaked material and use of suction in the operating theatre), hemostatic interventions used at the time of intrauterine balloon tamponade or uterine artery embolization (the number of uterotonic agents given [including oxytocin, ergometrine, misoprostol, and sulprostone], the administration of non-uterotonic agents [tranexamic acid, fibrinogen concentrate, and recombinant factor VIIa], and number of packed red blood cells, fresh frozen plasma, and platelets transfused), and other surgical interventions that had already been applied at the time of intrauterine balloon insertion or uterine artery embolization (composite of B-Lynch suture and uterine artery ligation). These clinically relevant characteristics were a priori selected based on literature[4, 5, 7, 12, 13, 18-23] and clinical reasoning. Missing variables were imputed using median and logically derived imputation (see Appendix 1 for the rationale behind the imputation method applied per missing variable).

To balance all characteristics over the course of persistent postpartum hemorrhage, estimated blood loss was stratified into increments of 500mL and women were matched within the same increment of blood loss in which they had the intervention. Thus, women who had intrauterine balloon tamponade during persistent postpartum hemorrhage were matched to women with *the same chance* (i.e. same propensity score) of receiving intrauterine balloon tamponade, but who underwent uterine artery embolization instead within the same increment of blood loss at the time of intervention. By matching in the same increments of blood loss, we ensured that women who had intrauterine balloon tamponade were matched to women who had uterine artery embolization at approximately the same amount of blood loss. Matching was performed by a 1:1 sequential greedy algorithm without replacement using a calliper of 0.2 times the standard deviation of the logit of the propensity score.[24] Balance in distribution of clinically relevant characteristics between both groups was assessed by standardized differences,

where distributions of characteristics were considered comparable when the standardized difference was less than 10% after propensity score matching.[25, 26] Interaction terms were included in the propensity score model if they improved balance between the comparison groups after propensity score matching.[27]

The primary outcome was compared between women who were managed by intrauterine balloon tamponade and women who underwent uterine artery embolization using a logistic regression model, resulting in estimated odds ratios (OR) with 95% confidence intervals (CI).[28] Differences in secondary outcome measures were estimated by Mann-Whitney U testing before propensity score matching, and by the Wilcoxon signed-rank test after propensity score matching, where a two-tailed p-value less than 0.05 was considered statistically significant.[29] To evaluate the robustness of our study findings with regard to propensity score matching, a sensitivity analysis was performed of the primary outcome measure by including the propensity score as a covariate in the logistic regression model to compare the primary outcome measure between both intervention groups, under the assumption that the propensity score has a linear functional relation with the log odds of the primary outcome.[30]

All continuous variables were summarised as medians with interquartile ranges (IQR), and categorical variables were presented as frequencies with percentages (%). All statistical analyses were performed using the Stata Statistical Software: Release 14 (College Station, TX: StataCorp LP, USA). The statistical analysis plan was approved by the Scientific Committee of the Sanquin Center for Clinical Transfusion Research before execution of the analyses.

Ethical approval

The TeMpOH-1 study was approved by the Ethical Committee of the Leiden University Medical Centre (P12.273, 2013) and by the institutional review boards of all participating hospitals. The TeMpOH-1 study was registered in the Netherlands Trial Register (Trial NL3909, 2013) and need to obtain informed consent was waived by the ethics committee.

RESULTS

Of the 270 101 women who gave birth in the Netherlands during the two-year inclusion period, 1391 women endured postpartum hemorrhage and fulfilled the inclusion criteria of the TeMpOH-1 study, of whom 1260 had ongoing hemorrhage despite first-line therapy combined with at least one uterotonic agent. We identified a total of 373 women who were initially managed by intrauterine balloon tamponade and 82 women who initially had uterine artery embolization at an estimated blood loss between 1000-7000mL to control bleeding. Eleven balloons were inserted below 1000mL of blood loss and five women underwent uterine artery embolization at a blood loss >7000mL. Out of the 373 women who initially had intrauterine balloon tamponade, 50 were propensity score matched to 50 of 82 women who initially underwent embolization during persistent postpartum hemorrhage (Figure 1).

Comparison of characteristics

Clinically relevant characteristics of women who were managed by intrauterine balloon tamponade and uterine artery embolization before and after propensity score matching are presented in Table 1. Before propensity score matching, multiple characteristics differed significantly between intervention groups, as indicated by a standardized difference above 10%. Women who were initially managed by intrauterine balloon tamponade were more likely to have a vaginal birth (80% vs 60% of women in the embolization group), and had less blood loss at the time of balloon insertion (median 2500mL [IQR; 2000 to 3000]) compared with women who initially had uterine artery embolization (median 3500mL [IQR; 3000 to 4500]). Furthermore, women who initially underwent uterine artery embolization were more likely to have coagulopathy (43% vs 11% of women in the balloon group), were more often treated with non-uterotonic agents, and received more blood components than women who were managed by intrauterine balloon tamponade. Uterine atony was the leading cause in both intervention groups. Characteristics were well balanced in the propensity score matched cohort, with standardized differences for all characteristics less than 10% (Table 1).

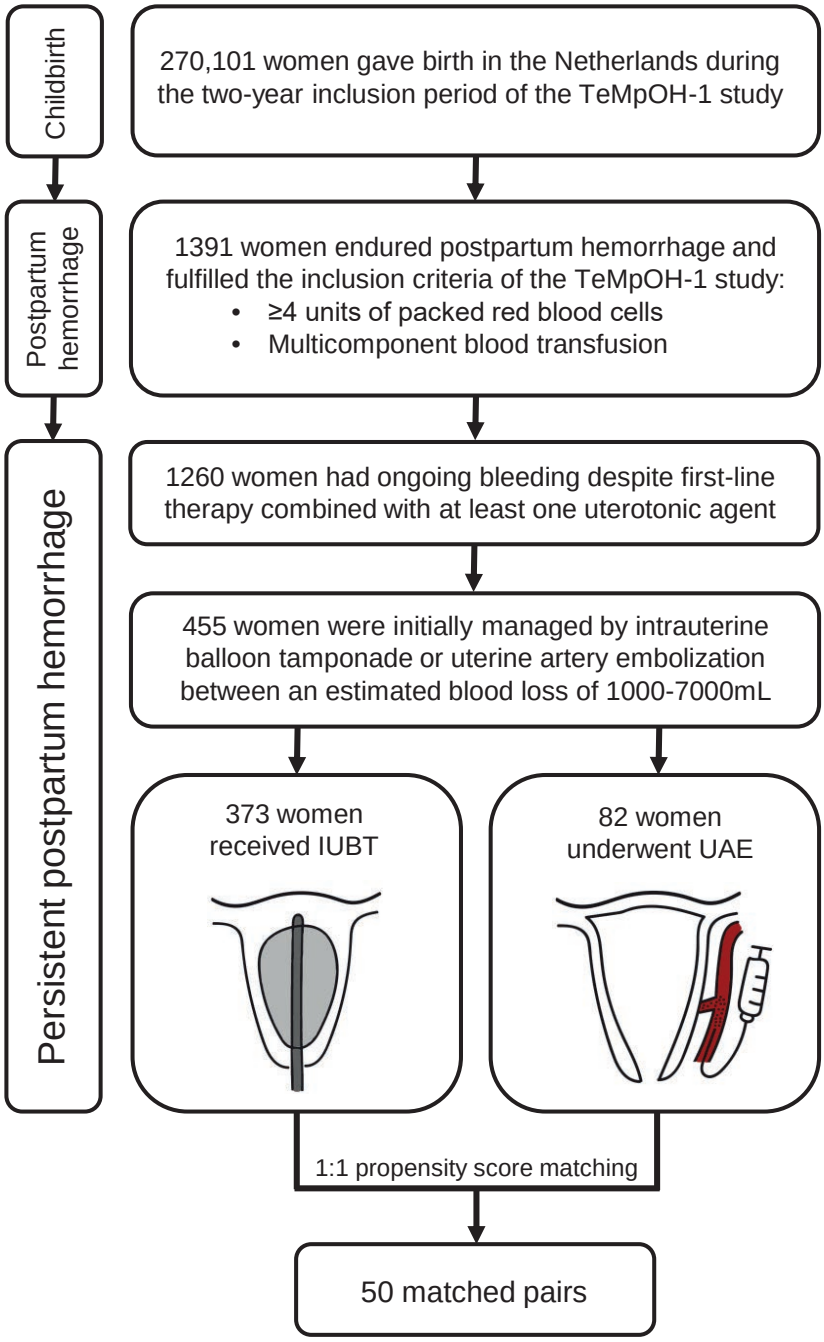

Figure 1. Flowchart of study enrolment and propensity score matching.
IUBT: Intrauterine balloon tamponade, UAE: Uterine Artery Embolization.

Table 1. Clinically relevant characteristics for women who had intrauterine balloon tamponade or who underwent uterine artery embolization between an estimated blood loss of 1000-7000mL because of persistent postpartum hemorrhage before and after propensity score matching.

	Before PS matching	
	IUBT N=373	UAE N=82
Maternal age, years*	31 (28-35)	32 (29-36)
Gestational age, weeks*	39 (38-40)	38 (37-40)
Multiparity, n (%)	170 (46)	43 (52)
Preeclampsia, n (%)	36 (10)	10 (12)
Multiple pregnancy, n (%)	23 (6)	6 (7)
Prior cesarean birth, n (%)	44 (12)	16 (20)
Mode of birth, n (%)	-	-
Vaginal delivery	300 (80)	49 (60)
Cesarean section	73 (20)	33 (40)
Cause of hemorrhage, n (%)	-	-
Uterine atony	293 (79)	53 (64)
Retained placenta	45 (12)	7 (9)
Abnormally invasive placenta	24 (6)	7 (9)
Other causes	11 (3)	15 (18)
Placental abruption	*2*	*1*
Placenta previa	*2*	*3*
Uterine rupture	*7*	*11*
Estimated blood loss at the time of the intervention, mL*	2500 (2000-3000)	3500 (3000-4500)
Coagulopathy, n (%)	42 (11)	35 (43)
Symptoms of shock, n (%)	304 (82)	68 (83)
Number of uterotonics given*	2 (2-3)	2 (1-3)
Non-uterotonic agents, n (%)	-	-
Tranexamic acid	132 (35)	42 (51)
Fibrinogen concentrate	6 (2)	13 (16)
Recombinant factor VIIa	3 (1)	3 (4)
Blood components*	-	-
Packed red blood cells	1 (0-2)	4 (3-7)
Fresh frozen plasma	0 (0-1)	2 (1-4)
Platelets transfusion	0 (0-0)	0 (0-1)
Surgical interventions, n (%)	3 (1)	2 (2)
B-Lynch suture	*3*	*2*
Uterine artery ligation	*0*	*1*

PS: Propensity Score, IUBT: Intrauterine Balloon Tamponade, UAE: Uterine artery embolization, SMD: Standardized Mean Difference, Ref: Reference.
*Reported as median with (interquartile ranges).

	After PS matching		
SMD (%)	IUBT N=50	UAE N=50	SMD (%)
15.6	32 (29-37)	31 (29-36)	5.7
28.9	39 (37-40)	38 (37-40)	6.9
16.8	28 (56)	27 (54)	4.0
7.5	6 (12)	6 (12)	0.0
7.1	4 (8)	4 (8)	0.0
22.4	9 (18)	10 (20)	5.0
54.0	-	-	0.0
-	28 (56)	28 (56)	-
-	22 (44)	22 (44)	-
-	-	-	-
Ref	32 (64)	33 (66)	Ref
6.6	5 (10)	5 (10)	0.0
19.2	6 (12)	6 (12)	0.0
34.7	7 (14)	6 (12)	5.9
-	*2*	*0*	-
-	*2*	*1*	-
-	*3*	*5*	-
62.5	3250 (2500-4000)	3250 (2500-4000)	0.0
60.4	18 (36)	18 (36)	0.0
1.3	40 (80)	41 (82)	5.0
28.0	2 (1-2)	2 (1-3)	5.2
-	-	-	-
13.5	23 (46)	21 (42)	8.0
30.0	4 (8)	4 (8)	0.0
10.1	1 (2)	1 (2)	0.0
-	-	-	-
88.7	4 (2-6)	4 (2-5)	9.2
80.1	2 (0-2)	2 (0-2)	5.5
48.7	0 (0-0)	0 (0-0)	6.3
20.8	2 (4)	2 (4)	0.0
-	*2*	*2*	-
-	*0*	*1*	-

Table 2. Outcomes for women with persistent postpartum hemorrhage who initially received intrauterine balloon tamponade versus women who initially underwent uterine artery embolization between an estimated blood loss of 1000-7000mL after birth.

	Unadjusted analysis	
	IUBT (N=373)	UAE (N=82)
Composite primary outcome, n (%)	21 (5.5)	10 (12)
Peripartum hysterectomy	19 (5.0)	10 (12)
Maternal mortality	2 (0.5)	0 (0)
Secondary outcome measures*	-	-
Total number of packed cells, units	4 (3–7)	7 (5–11)
Total volume of blood loss, mL	3500 (3000–4500)	4500 (3350–6000)

IUBT: Intrauterine Balloon Tamponade, UAE: Uterine Artery Embolization, OR: Odds Ratio, MWU: Mann-Whitney U, WSR: Wilcoxon signed-rank.
*Reported as median with (interquartile ranges).

Comparison of outcomes

Among the 373 women who initially had intrauterine balloon tamponade, 262 women (70%) required no additional intervention and bleeding was adequately treated. After intrauterine balloon insertion, 12 women (3%) had a B-Lynch suture, four women (1%) had uterine artery ligation, and 81 women (22%) still had to undergo uterine artery embolization, of whom seven eventually underwent hysterectomy. The total number of women who had a peripartum hysterectomy after intrauterine balloon tamponade was 19 (5%) and two women (0.5%) died because of exsanguination before additional interventions could be performed. Of the 82 women who initially underwent uterine artery embolization, 14 women (17%) endured ongoing hemorrhage, of whom three (4%) had a B-Lynch suture, one (1%) had uterine artery ligation, and ten (12%) required peripartum hysterectomy. None of the women who primarily had uterine artery embolization died. In the unadjusted analysis, the risk of the composite primary outcome (peripartum hysterectomy and or maternal mortality) was higher for women who underwent uterine artery embolization compared to women who received intrauterine balloon tamponade (12% vs 5.5% [OR 2.33, 95% CI; 1.05 to 5.15]). In addition, total volume of blood loss (median 4500mL [IQR; 3350 to 6000] vs 3500mL [IQR; 3000 to 4500] respectively, p<.001) and total number of packed red blood cells transfused (median 7 units [IQR; 5 to 11] vs 4 units [IQR; 3 to 7] respectively, p<.001) were higher for women who underwent uterine artery embolization compared to women who had an intrauterine balloon as initial management during persistent postpartum hemorrhage (Table 2). Of all women who had uterine

	Propensity score matched adjusted analysis		
OR (95% CI)	IUBT (N=50)	UAE (N=50)	OR (95% CI)
2.33 (1.05–5.15)	6 (12)	6 (12)	1.00 (0.30–3.34)
-	6 (12)	6 (12)	-
-	0 (0)	0 (0)	-
MWU p-value	-	-	WSR p-value
<.001	7 (5–10)	6 (4–9)	0.319
<.001	4500 (3600-5400)	4000 (3250-5000)	0.382

artery embolization (82 as initial management and 81 after intrauterine balloon tamponade), three (1.8%) suffered an embolization-related thrombo-embolic event, of whom one had received intrauterine balloon tamponade before embolization was performed.

In the propensity score matched cohort, 29 of the 50 women (58%) who were initially managed by an intrauterine balloon required no additional intervention to control bleeding. Two women (4%) had a B-Lynch suture after intrauterine balloon insertion and 15 (30%) underwent uterine artery embolization after intrauterine balloon tamponade, of whom two required hysterectomy. The total number of women who underwent hysterectomy to arrest hemorrhage was 6 (12%) for both women who initially had intrauterine balloon tamponade and women who initially had uterine artery embolization. Maternal deaths occurred in neither of the intervention groups. In the propensity score matched adjusted analyses, there was no significant difference in the risk of the composite primary outcome between the intervention groups (12% in each group [OR 1.00, 95% CI; 0.30 to 3.34]). Neither did total volume of blood loss (median 4500mL [IQR; 3600 to 5400] vs 4000mL [IQR; 3250 to 5000] respectively, p=0.382) or total number of packed red blood cells transfused (median 7 units [IQR; 5 to 10] vs 6 units [IQR; 4 to 9] respectively, p=0.319) differ significantly between both women who had intrauterine balloon tamponade and women who underwent uterine artery embolization (Table 2). One woman in the propensity score matched cohort had a thrombo-embolic event related to the uterine artery embolization performed after initial management with intrauterine balloon tamponade failed.

Sensitivity analysis

The sensitivity analysis yielded results similar to our primary analysis. When the propensity score was used as the only covariate in the logistic regression model to compare the primary outcome measure between all women who had intrauterine balloon tamponade (N=373) and all women who underwent uterine artery embolization (N=82) as the initial management for persistent postpartum hemorrhage between an estimated blood loss of 1000 to 7000mL, the risk of the composite primary outcome was slightly, but still not statistically significant, lower among women who were managed by intrauterine balloon tamponade compared to women who underwent uterine artery embolization (OR 0.77, 95% CI; 0.27 to 2.21).

DISCUSSION

This propensity score matched cohort study found no significant difference in the risk of the composite outcome of hysterectomy and/or maternal death between women with persistent postpartum hemorrhage and who were initially managed by intrauterine balloon tamponade or uterine artery embolization between a blood loss of 1000 and 7000mL. Neither did we find significant differences in total volume of blood loss and total number of packed red blood cells transfused. Thirty-four percent (17/50) of the women who were initially managed by an intrauterine balloon tamponade had an additional intervention, of whom 15 had uterine artery embolization. One woman suffered an embolization-related thrombo-embolic event.

To the best of our knowledge, this is the first study comparing the effect of intrauterine balloon tamponade with another invasive management strategy to control bleeding and avert peripartum hysterectomy and maternal death during persistent postpartum hemorrhage. By using propensity score matching, we ensured a similar distribution of potential confounding variables between the two intervention groups. The definition of persistent postpartum hemorrhage enabled us to overcome differences between caregivers regarding estimation of blood loss and establish a clear point in time at which an additional intervention (i.e. intrauterine balloon tamponade or uterine artery embolization) was deemed necessary following failure of initial management. Another key strength is that the composite primary outcome consisted of two postpartum hemorrhage-related core outcome sets (peripartum hysterectomy and maternal death), allowing our results to be potentially included in systematic reviews or meta-analyses on persistent postpartum hemorrhage.[31] Furthermore, the extensive TeMpOH-1 database made it possible to include many characteristics as potential confounders in the propensity score model. Nonetheless, even though this is the first study that compares the effectiveness of intrauterine balloon tamponade to another invasive management strategy, our propensity score matched sample size was limited to 50 pairs. This resulted in confidence intervals too broad to rule out type II error for the composite primary outcome measure between both intervention groups. Limited statistical power also restricted possible comparative analyses of subgroups to determine which characteristics may modify the effect of intrauterine balloon tamponade. However, consistency between the results of our primary analysis and the sensitivity analysis strengthens the credibility of our findings. Nevertheless, our results should be interpreted with caution considering several other limitations in relation to the observational design. We

were unable to collect data regarding type of intrauterine balloon device inserted, volume of fluid used to inflate the intrauterine balloon, and the reason of failure of intrauterine balloon tamponade or uterine artery embolization. Additionally, although we are confident to have included all clinically relevant characteristics associated with the clinical decision to use intrauterine balloon tamponade or uterine artery embolization, residual confounding cannot be ruled out. Finally, women were included when in need of four or more units of packed red blood cells or a multicomponent blood transfusion, and who had an estimated blood loss of 1000 to 7000mL at the time of intervention. Our results can therefore not be generalized to all women who satisfy the criteria for persistent postpartum hemorrhage, but are still applicable to the large majority in settings where both interventions and packed cells are available.

Intrauterine balloon tamponade has been incorporated as a management option into multiple national guidelines for postpartum hemorrhage.[32-35] In non-comparative studies, success rates of intrauterine balloon tamponade to control bleeding after birth varied between 67% to 91%.[6, 12, 13, 36] However, evidence for the benefits of intrauterine balloon tamponade compared to other invasive management strategies is lacking, resulting in uncertainty whether intrauterine balloon tamponade is effective during the course of persistent hemorrhage.[37]

Our reported success rate of 70% among all women who were initially managed by an intrauterine balloon tamponade between an estimated blood loss of 1000 to 7000mL is in accordance with prior literature. However, success rate of women who had intrauterine balloon tamponade and required no additional intervention to control hemorrhage was 58% in the propensity score matched cohort. The explanation for this apparent lower success rate could be due to the difference in severity of bleeding. Volume of blood loss at time of intrauterine balloon insertion was lower for the total cohort of women who had intrauterine balloon tamponade (median 2500mL [IQR; 2000 to 3000]) compared to women in the propensity score matched cohort (median 3250mL [IQR; 2500 to 4000]). This is due to the fact that we matched women who had intrauterine balloon tamponade with women who had uterine artery embolization within the same increment of blood loss at the time of the intervention. Consequently, there were proportionally more women with intrauterine balloon tamponade in the propensity score matched cohort who had more severe bleeding than in the total cohort of women who were initially managed by intrauterine balloon tamponade. Nevertheless, early timing of intrauterine balloon tamponade during the course of postpartum hemorrhage has been associated with improved maternal outcome, whereas early timing

of uterine artery embolization seems to be unrelated to maternal outcome.[19, 38] However, in these studies, early timing of intrauterine balloon tamponade in absence of a control group could also have led to an overestimation of the effectiveness due to the possibility that the use of intrauterine balloon tamponade was not absolutely necessary.

Nevertheless, although 34% of women who initially received intrauterine balloon tamponade had an additional intervention, there was no significant difference in the risk of peripartum hysterectomy and or maternal death compared to women who initially underwent uterine artery embolization. Therefore, our results indicate that initial management by intrauterine balloon tamponade during persistent postpartum hemorrhage has the potential to control bleeding and obviate the need for uterine artery embolization in most women, without an increased risk of severe maternal outcome. By using intrauterine balloon tamponade as intervention of first choice during persistent hemorrhage, a majority of women can be spared a more invasive and expensive intervention, i.e. embolization. Two studies corroborate our study findings, reporting a significant drop in the number of invasive procedures following introduction of intrauterine balloon tamponade into their guidelines on the management of postpartum hemorrhage after an initial treatment with uterotonic agents failed.[39, 40]

However, since our propensity score matched sample size was small, we can only make cautious statements regarding the effect of both management options on the risk of hysterectomy and or maternal mortality. Furthermore, it is specifically important to note that if uterine artery embolization was not available, it is possible that a larger proportion of women who were initially managed by intrauterine balloon tamponade had hysterectomy or died. In addition, although intrauterine balloon tamponade seems to be a readily available intervention of first choice in the management of persistent postpartum hemorrhage, it should not delay or be considered as replacement for embolization or hysterectomy if that procedure is deemed necessary to control bleeding. On the other hand, balloon tamponade could also be used as temporizing measure while awaiting embolization or surgery.[41]

The World Health Organisation acknowledges the need for further research into the efficacy of intrauterine balloon tamponade in the management of postpartum hemorrhage.[42] Considering that uterine artery embolization is not widely available, comparative research of intrauterine balloon tamponade to other management strategies is warranted, particularly in low-resource settings where

intrauterine balloon tamponade could be used as cost-saving option to control ongoing bleeding. One randomized trial evaluated the effectiveness of intrauterine balloon tamponade as an adjunct to misoprostol, but was underpowered to demonstrate a significant treatment effect.[43] This inability to resolve the research question whether intrauterine balloon tamponade is as good as or superior to other management strategies due to small sample sizes, highlights the need for larger studies comparing intrauterine balloon tamponade to other management strategies for a good substantiated implementation of intrauterine balloon tamponade into the guidelines for management of postpartum hemorrhage. International research collaboration may be the key to overcome the problem of low statistical power and determine whether and when intrauterine balloon tamponade should be used during the course of postpartum hemorrhage. Our study design provides a useful framework and could serve as a starting point for future comparative effectiveness research of intrauterine balloon tamponade to control intractable postpartum hemorrhage in clinical as well as observational studies.

CONCLUSION

The risk of the composite outcome of peripartum hysterectomy and/or maternal death, total volume of blood loss, and total number of packed red blood cells transfused did not significantly differ between women who had intrauterine balloon tamponade and women who had uterine artery embolization as initial management for persistent postpartum hemorrhage. Intrauterine balloon tamponade seems to be a readily available intervention of first choice in the management of persistent postpartum hemorrhage that could obviate the need for uterine artery embolization in most women. However, limited sample size made it difficult to demonstrate equivalence between both interventions and our results emphasize the need for larger studies comparing intrauterine balloon tamponade to other management options for a substantiated implementation of balloon tamponade into clinical guidelines for management of postpartum hemorrhage.

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SUPPLEMENTALS

Table S1. First-line therapy as defined per primary cause of hemorrhage[15]

Primary cause of hemorrhage	*Corresponding first-line therapy*
Uterine atony	Administration of uterotonic agents with or without inspection of the uterine cavity
Retained placenta(l) (remnant)	Manual removal of the placenta(l) (remnant)
Placenta previa with/without accreta	Cesarean section
Placental abruption	Cesarean section*
Traumatic cause	Surgical repair
Surgical cause	Surgical repair

*In case of stillbirth no cesarean section was performed, a vaginal birth was then pursued.

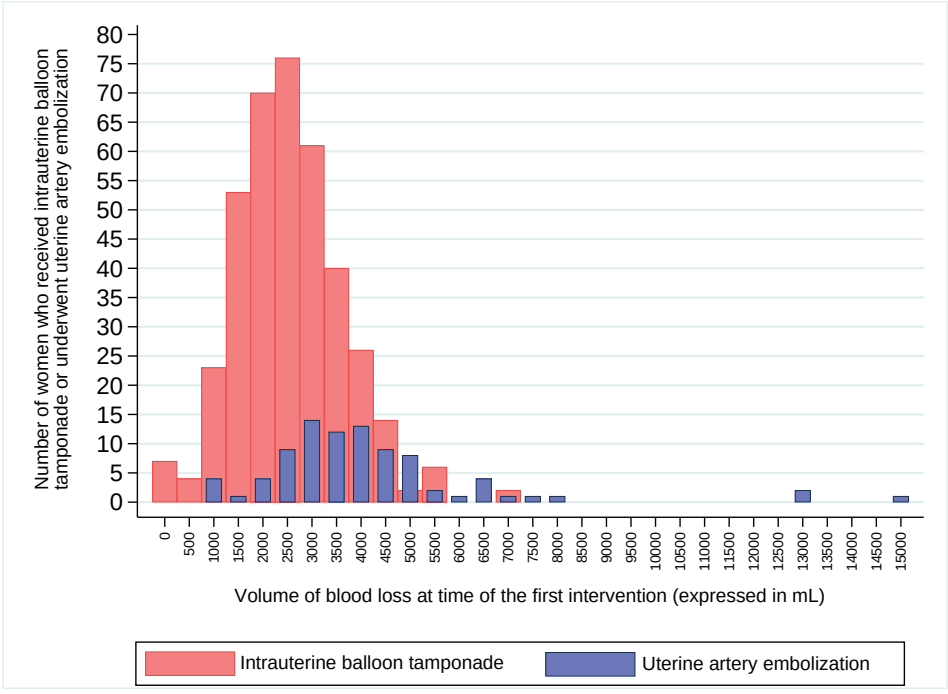

Figure S1. Number of women with persistent postpartum hemorrhage and who were initially managed by intrauterine balloon tamponade or uterine artery embolization according to volume of blood loss at the time of intervention (stratified into increments of 500mL).

APPENDIX 1

Out of the 373 women who were initially managed by intrauterine balloon tamponade at an estimated blood loss between 1000 to 7000mL, 11 women (3%) had only one of the following variables missing: prior cesarean birth (N=3), gestational age (N=3), mode of birth (N=2), multiple pregnancy (N=2), and parity (N=1). Only prior cesarean birth was missing for one of 82 women (1%) who initially underwent uterine artery embolization. Missing data for gestational age were imputed using median imputation and all other missing variables were logically derived from information in the TeMpOH-1 database.

Median imputation:
Gestational age (N=3): In the absence of a clear deterministic approach to estimate pregnancy duration based on other available characteristics and because of the small number of missing, we replaced missing values with the median gestational age of all women who had intrauterine balloon tamponade between 1000 to 7000mL of blood loss. The median of 39 weeks (interquartile range: 38 to 40 weeks) was chosen due to the non-normal distribution of gestational age.

Logically derived imputation:
Prior cesarean birth (N=4): It was assumed that none of the women had a prior cesarean birth. Two women were primigravida, and the other two women had a planned home birth, but were transferred to the hospital during labour. Considering that women in the Netherlands will give birth under guidance of an obstetrician during the consecutive pregnancies when they have a cesarean section in the past, it was assumable that these women had no prior cesarean birth.

Mode of birth (N=2): According to free-text fields in the TeMpOH-1 database, both women had a vaginal birth. One woman had a planned home birth and was referred to the hospital because of postpartum hemorrhage, while the other woman had a vaginal birth in the hospital, which was followed by a manual removal of the placenta.

Multiple pregnancy (N=2): Both women were assumed to have no multiple pregnancy. In the Netherlands, multiple pregnancy is an indication to have prenatal check-ups in the hospital. Both women had no such indication, making it unlikely that these women had a multiple pregnancy.

Parity (N=1): This woman was classified as a primigravida in the TeMpOH-1 database. Therefore, we considered her as a nulliparous woman.