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Does the use of chitosan covered gauze for postpartum hemorrhage reduce the need for surgical therapy including hysterectomy? A databased historical cohort study

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Abstract

Objectives: Postpartum hemorrhage (PPH) is still one of the leading causes of maternal mortality worldwide. Recently effective PPH therapy with uterine packing with the chitosan-covered gauze was shown. This databased retrospective case–control study compares the therapy success of the chitosan tamponade with that of the balloon tamponade and medical therapy only.

Methods: All women who delivered at a university hospital between May 2016 and May 2019 with PPH were included. Based on the applied therapy, women were divided into three groups: medical therapy only, balloon tamponade and chitosan tamponade. The groups were compared in terms of therapy success, side-effects and reasons for PPH. Primary outcome was the need for surgical/radiological measures including hysterectomy, secondary outcomes were differences in hemoglobin levels, duration of inpatient stay, admission to intensive care unit, number of administered blood products and inflammation parameters.

Results: A total of 666 women were included in the study. 530 received medical therapy only, 51 the balloon tamponade and 85 the chitosan tamponade. There were no significant differences in the need for surgical therapy, but a significantly lower number of hysterectomies in the chitosan tamponade group than in the balloon tamponade group. There were no relevant differences in secondary outcomes and no adverse events related to the chitosan tamponade. Since the introduction of chitosan tamponade, the number of PPH related hysterectomies dropped significantly by 77.8%.

Conclusions: The chitosan tamponade is a promising treatment option for PPH. It reduces the postpartum hysterectomy rate without increased side effects compared to the balloon tamponade.

Keywords: balloon tamponade; chitosan covered gauze; combat gauze; peripartum hemorrhage (PPH); uterine packing.

Introduction

Postpartum hemorrhage (PPH) is the primary cause of maternal morbidity and mortality worldwide [1]. It is responsible for about 30% of maternal deaths in low-income countries and for 13% in industrialized countries [2]. Therapy options vary with the degree of severity from medical therapy over uterine packing techniques to surgical measures: compressing sutures, selective devascularization and postpartum hysterectomy (HE), the last therapeutic resort associated with high morbidity and the loss of fertility [3].

Medical therapy is the first line therapy in PPH and consists of the use of uterotonic and hemostatic drugs. In cases of persistent bleeding uterine packing is an option to control hemorrhage and prevent surgical therapy.

A well-established uterine tamponade is the balloon tamponade (BT). It was designed to control PPH by compressing the placental bed and reduction of the uterine perfusion pressure [4]. Its safety and effectiveness are well accepted [4–6].

Recently, uterine packing with chitosan covered gauze (chitosan tamponade, CHT) has been introduced as a treatment option for PPH. In 2012, the first successful use of CHT in a case of severe PPH was reported, in which the seemingly unavoidable HE could be prevented [7]. Several case reports and one historical cohort study showed

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promising results in terms of therapy success including a HE-rate reduction of 50–75% [8–11].

Chitosan is an effective hemostatic agent and was designed for treatment of bleeding war injuries [12]. It is a hydrophilic bipolymer resulting from deacylation of chitin, part of crustaceans crusts [13]. Hemostasis is achieved by electrostatic interactions between the erythrocytic cell membrane and chitosan. It works independently of the coagulation cascade, in the presence of heparin and under hypothermic conditions [14]. Its safety for people with crustacean allergies has been proven [15].

Based on these results and characteristics, CHT was introduced in May 2016 in the Department of Obstetrics, Charité University Hospital in Berlin, Germany. It was used as an alternative to the BT in cases refractory to medical therapy only.

This data-based historical case-control study includes the medical data of all women who were treated for PPH at this department since the introduction of CHT. Based on the applied treatment option, the women were divided into three groups: medical therapy only (A), BT (B) and CHT (C). The groups were compared in terms of therapy success, defined as bleeding control without further surgical/radiological measures, and safety. The primary outcome was the need for surgical/radiological therapy including compressing sutures, selective devascularization, (re-) laparotomy and HE.

Materials and methods

Medical records of all women with PPH who delivered at the Department of Obstetrics, Charité University Hospital, between May 2016 and May 2019 were reviewed. Women <18 years, <20 weeks of gestation and patients with planned cesarean HE due to placenta percreta were excluded. Women who received both tamponades (BT and CHT) simultaneously or one after another were excluded from statistical analysis. All records were reviewed again in May 2020 for subsequent pregnancies and long-term side-effects. The historic cohort study received its approval by the ethical committee (EA2/229/20).

PPH was defined as a blood loss ≥500 mL after vaginal delivery (VD)/≥1,000 mL following cesarean section (CS) and was divided into three degrees of severity based on the blood loss and adjusted to the birth mode:

- Grade I: 500–999 mL after VD, 1,000–1,499 mL after CS.
- Grade II: 1,000–1,499 mL after VD, 1,500–1,999 mL after CS.
- Grade III: ≥1,500 mL after VD, ≥2,000 mL after CS.

Blood loss was estimated by using a collection device [16], which was placed by the obstetrician on call in the moment when increased bleeding became apparent.

All patients were treated according to the German–Austrian–Swiss management guidelines [17], providing an algorithm with four subsequent therapy steps:

- Step I: Use of uterotonic drugs like oxytocin or carbetocin and possibly misoprostol (off label use).
- Step II: Switch to sulproston, administration of tranexamic acid and, if necessary, fibrinogen. Depending on the hemostatic state, transfusion of blood products (fresh frozen plasma [FFP], red blood cell concentrates [RBC]).
- Step III: Insertion of a BT into the uterine cavity and inflation under sonographic guidance to apply pressure to the uterine wall and control the bleeding. In this study the Bakri postpartum balloon was used [18]. Continuation of the sulproston therapy. Deflation and removal of the balloon after 12–24 h. In case of ongoing/recurrent hemorrhage step IV is indicated.
- Step IV: Surgical/radiological intervention such as compressing sutures, embolization/ligation of the uterine arteries, segmental uterine resection or HE.

In May 2016, CHT was introduced at the Department of Obstetrics as a potential alternative to the BT for uterine packing (step III). Initially, it was used exclusively as the last attempt therapy when HE or other life-threatening complications were imminent, as CHT is not approved for internal use (off-label-use). The final decision on the application was taken by the senior obstetrician in charge. This approach entails the risk of selection bias. However, due to good experience regarding its effectiveness, the CHT was then used more frequently and earlier in the course of disease after obtaining patients informed consent. The gauze was inserted transvaginally into the uterine cavity under ultrasound guidance after VD, transabdominally after CS. The end of the tamponade was led out of the cervix into the vagina for removal. The length and number of the used tamponade was dependent on size and tonus of the uterus. In this study Celox™ was used, one tamponade is 3 m long, 7.6 cm wide [12]. The end of tamponade was marked by a stitched suture (No. 1 Vicryl). Patients received a wristband for identification and antibiotic prophylaxis with a second-generation cephalosporin until removal after 12–24 h.

Information about cause, treatment and outcome of PPH and demographic and epidemiological data were collected from the medical records of all women with PPH. Based on the applied treatment, the women were divided into three groups. Women who were treated with medical therapy only were group A, those with BT group B and those with CHT group C.

Primary outcome was the need for surgical (and radiological) therapy (step IV) including compressing sutures, ligation/embolization of the uterine arteries, (re-)laparotomy and HE. The number of HE's before introduction of CHT was compared with a comparable period afterward. Secondary outcomes were differences in hemoglobin levels, duration of inpatient stay, admission to intensive care unit (ICU), number of administered blood products and inflammation parameters.

Due to the therapy algorithm, which starts with medical therapy (step I, step II) before uterine packing (step III) is recommended, more, and a higher percentage of milder cases of PPH were expected to be in group A, and fewer, but more severe cases in group B and C. Nevertheless, severe cases in which step IV was necessary were also expected in group A, which is why this group was included.

Statistical analysis

Binary logistic regression was used to analyze the probability for step IV. Group C was the reference group. Logistic regression was also used

for binary secondary outcomes. To obtain comparable results between group A and the other two groups, it was necessary to adjust the calculation to the severity of PPH. Whenever sensible, results were adjusted for blood loss in mL, which appears to be the best marker for the severity of PPH. Results were also adjusted for confounders, identified by sensitivity analysis.

When adjustment for blood loss was not sensible (e.g., drop in hemoglobin, administered blood products), in cases of non-binary outcomes and for less than 10 events, only group B and C were compared.

Demographic and epidemiological data and outcomes without adjustment were compared using compatible univariate analysis (e.g., the independent-samples t-test, chi-squared test, Mann–Whitney-U test, Fisher's exact test). In the first steps, all groups were tested together (first result in the right column), when the test was significant, every group was tested with every other group ($P^{A/B}$=p-value for group A vs. group B, $P^{A/C}$=p-value for group A vs. group B, $P^{B/C}$=p-value for group B vs. group C). The change in HE rate was calculated using the odds ratio.

Statistical significance was accepted for $p<0.05$. Statistical analysis was performed using IBM SPSS Version 26 (IBM Corp. Armonk, NY, USA). Tables and graphs were created by the authors with Microsoft PowerPoint or Word, version 16.45.

Results

From May 2016 until May 2019, 695 out of 16,693 women who delivered at the Department of Obstetrics, Charité University Hospital, developed PPH (4%). After exclusion of those having received both tamponades (n=11) and those with planned cesarean HE (n=18), 666 women were included. In total, 530 women (79%) received medical therapy only (A), the other 136 required uterine packing. 51 (8%) received the BT (B), 85 (13%) the CHT (C). In nine cases two CHT's were used, in one case three. See flow diagram (Figure 1).

Primary cause of PPH was uterine atony, responsible for 73% of the cases. In 17%, it occurred in combination with retained placental tissue, in 5%, in combination with increased bleeding from obstetric injury. In 9 cases (1%), PPH occurred more than 2 h after childbirth. For further information, see Figure 2.

In 48% of the cases women had a PPH grade I, in 28% grade II and in 24% grade III. Most women in group A showed PPH I (56%), whereas the majority of group B and C showed PPH III (67%, 59%). There were also cases of uterine tamponade in the PPH I group and medical therapy only for grade III. Blood loss was the highest in group B and lowest in group A with no significant difference between group B and C (p-value=0.580). For detailed information, see Table 1.

Statistical analysis showed demographic differences between the groups. Women of group A were significantly younger than women in the other two groups and received less frequently CS. Gestational age in group A was significantly higher than in group C. Age and mode of birth were identified as confounders and therefore adjusted for in further analysis. See Table 2 for further information and p-values.

Step IV was necessary in 34 (5%) of all women. In 18 (3%) of group A, 8 (16%) of group B and also 8 (9%) of group C.

Success rate of group C, defined as bleeding control without further measures, was 91%, success rate of group B was 84%. After vaginal delivery, success rate in group C was 98%, (one out of 50 patients required step IV), vs. 92% in group B (2 out of 25 patients required step IV). After CS success rate in group C was 80% (7 out of 35 patients required step IV), vs. 77% in group B (6 out of 26 patients required step IV).

Binary logistic regression showed an odds ratio of 2.208 for the risk of needing step IV for group A in comparison to group C and an odds ratio of 1.044 for group B compared to group C, which is not significant (p=0.164, p=0.950). Group A had a lower risk for being administered to ICU than group C (OR 0.367/p-value <0.001), without significant differences between group B and C (Table 3).

No differences were detected for drop in hemoglobin, lowest hemoglobin, number of administered blood products, inflammation parameters or the duration of the inpatient stay between group B and C (Table 4), Five (0.8%) of the included women required HE. Four in group B (8%), one in group A (0.2%) and none in group C (0%). The woman of group A did not receive additional PPH treatment as she underwent emergency cesarean section for amniotic fluid embolism and required a hysterectomy on the next day due to her deranged coagulation. There was a significantly lower HE-rate in group C than in group B (p=0.018, Fishers exact test). Additionally, in 31 months after the implementation of CHT (11/2016–05/2019) two HE's out of 9,167 births due to PPH were necessary, in 31 months before (04/2014–10/2016) nine HE's out of 9,058 births were performed Figure 3.

None of the women of group B and C showed signs of infection, sepsis or endometritis following therapy. Up to May 2020, we know of 25 subsequent pregnancies with good outcomes, defined as pregnancies without severe complications ending with the delivery of a healthy, carried-to-term baby. Seventeen in group A, five in group B and three in group C. Two further pregnancies ended in early abortions, one in group A and one in group C.

Eleven women received both tamponades. In three cases, CHT was used intravaginally in addition to the BT in order to prevent dislocation or for bleeding from the cervix.

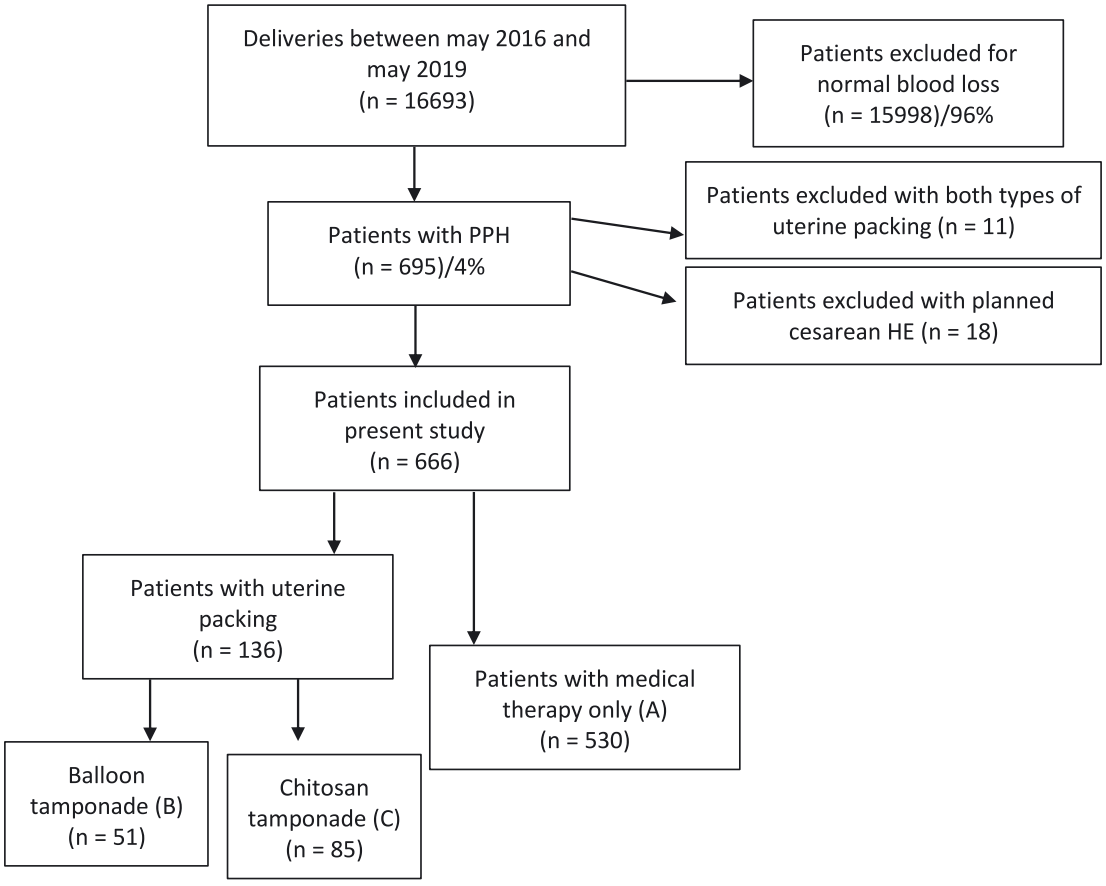

Figure 1: Flow diagram that shows the inclusion criteria of the patients and the assignment to the three groups.
PPH, postpartum hemorrhage; HE, hysterectomy.

In three cases, CHT was used after BT had failed, the other way around in one case. Four patients underwent uterine packing with both devices at the same time. Mean blood loss in this group was 3,045 mL, step IV was necessary in four cases (36%), HE in two cases (18%).

Discussion

This study investigated the effect of CHT on the need for step IV in PPH compared to medical therapy only and the BT. All surgical procedures for PPH treatment are associated with severe potential morbidity and should therefore be avoided if possible. Compression sutures carry the risk of uterine necrosis and endometritis [19, 20]. Selective devascularization can cause fistula formation between arteria and vena, intraligamentary hematoma, ureteral lesion and can cause uterine necrosis and infection in rare cases [2, 21]. Postpartum HE is associated with high morbidity, i.e., bladder injury in 6–12%, ureteral injuries from 0.4–41%, 2,000–3,000 mL mean blood loss, at least 1% maternal mortality rate and the loss of fertility [22, 23].

The reduction of the HE-rate due to PPH of 77.8% after the implementation of CHT in this study is therefore very relevant and supports the results of previous publications [8–10]. There is no doubt that this decline in hysterectomy rates is due to the introduction of CTH as there were no other changes in PPH treatment at our institution in the assessed time period. The significantly lower number of HE´s in group C compared to group B indicates, that CHT may be superior to the well-established and in the guidelines [24] recommended BT [5, 6, 25], as also concluded by Dueckelmann et al. [10].

These positive results may be caused by the combination of the balloons compressing mechanism with the coagulating properties of chitosan [26]. A major advantage is its clotting mechanism independently of the coagulation cascade, which even works in the presence of heparin [14], especially useful in severe cases with deranged hemostasis and consumption of coagulation factors.

Further advantages of CHT compared to BT are the lower price (appr. 60€ vs. 250€) [12, 18] and the easy application without reported risk for dislocation vs. the 10% dislocation rate of the BT [27]. Especially in low-

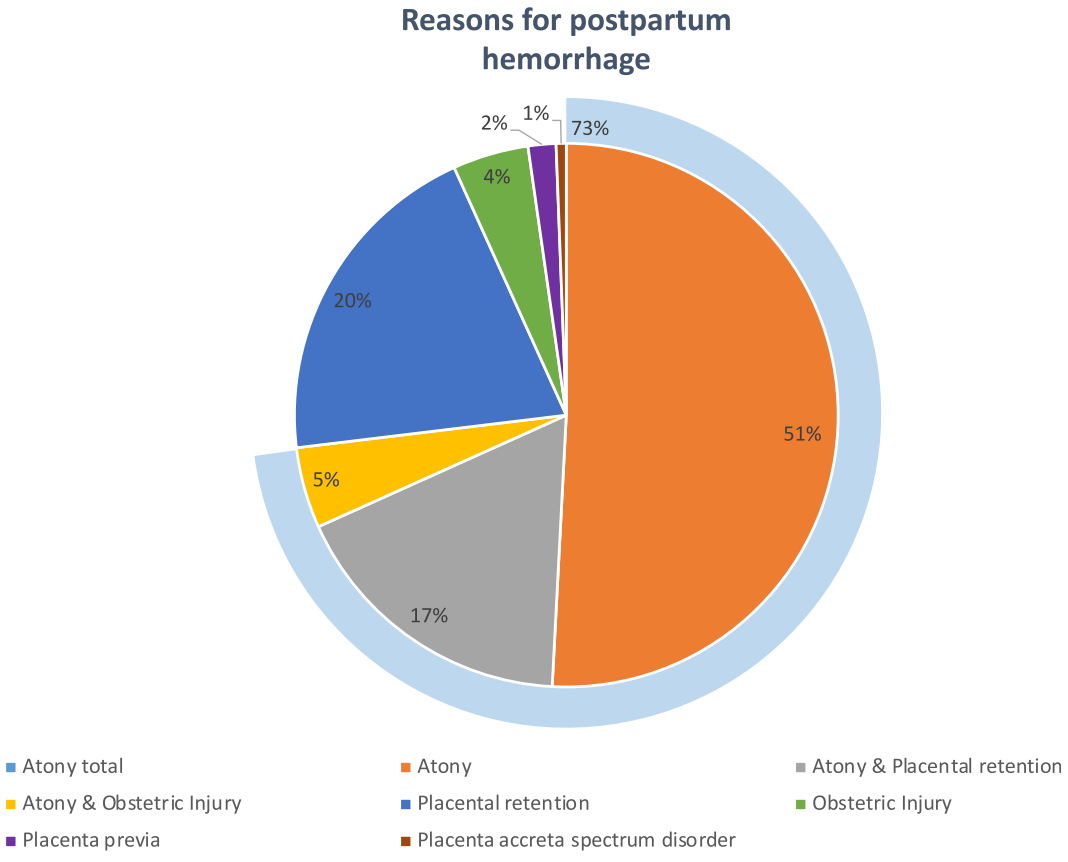

Figure 2: Reasons for PPH.

Table 1: Grade of PPH (postpartum hemorrhage) and blood loss in mL in groups A, B and C.

	A (medical therapy)	B (balloon tamponade)	C (chitosan tamponade)
PPH grade I	295 (55.7%)	8 (15.7%)	18 (21.2%)
Vaginal birth	261 (99.6%)	0 (0%)	1 (0.4%)
Cesarean section	34 (57.6%)	8 (13.6%)	17 (28.8%)
PPH grade II	157 (29.6%)	9 (17.6%)	17 (20.0%)
Vaginal birth	147 (92.5%)	3 (1.9%)	9 (5.6%)
Cesarean section	10 (41.7%)	6 (25%)	8 (33.3%)
PPH grade III	78 (14.7%)	34 (66.7%)	50 (58.8%)
Vaginal birth	61 (50.4%)	22 (18.2%)	38 (31.4%)
Cesarean section	17 (41.4%)	12 (29.3%)	12 (29.3%)
Blood loss, mL	1,008 ± 486	2,099 ± 1,062	1,828 ± 855

The cross table shows the absolute numbers and percentages of women from groups A, B and C and the respective degree of PPH, additionally subdivided for birth mode, and the mean blood loss in mL ± standard deviation for groups A, B and C. Vaginal birth includes spontaneous vaginal deliveries and operative vaginal deliveries (vacuum, forceps).

income countries, where mortality rates due to PPH are the highest and financial resources low, CHT could substantially improve quality of care [2, 7, 9, 10].

The high morbidity in the group with both tamponades shows that in very severe cases, all available options were used to stop hemorrhage. In cases refractory to one of the devices, the other one or a combination may be applied, as described before by our group [28]. The use of more than one CHT could also be an option in these situations. Due to the lack of data no reliable statement can be given.

The OR for step IV in group A compared to group C is not significant but shows a tendency in favor of CHT. It can

Table 2: Patient's demographics and reasons for PPH.

	A (n=530) medical therapy	B (n=51) balloon tamponade	C (n=85) chitosan tamponade	p-Value
Maternal age, years	30.4 ± 6.0	33.1 ± 6.3	32.2 ± 6.1	**0.001**^{A}
				P$^{A/C}$ 0.033
				P$^{A/B}$ 0.008
				P$^{B/C}$ 0.692
Gestational age, weeks	39.5 ± 3.1	38.8 ± 3.1	38.5 ± 3.6	**0.014**^{A}
				P$^{A/C}$ 0.019
				P$^{A/B}$ 0.356
				P$^{B/C}$ 0.782
Gravida	2 (1–3)	2 (1–3)	2 (1–3)	0.676^{KW}
Para	1 (1–2)	1 (1–2)	1 (1–2)	0.373^{KW}
Spontaneous delivery	409 (77.2%)	16 (41.4%)	45 (52.9%)	**<0.001**^{X}
				P$^{A/C}$ <0.001^{X}
				P$^{A/B}$ <0.001^{X}
				P$^{B/C}$ 0.014^{X}
Vacuum/Forceps	66 (12.5%)	9 (17.6%)	5 (5.9%)	0.389^{X}
Cesarean section	55 (10.4%)	26 (51.0%)	35 (41.2%)	**<0.001**^{X}
				P$^{A/C}$<0.001^{X}
				P$^{A/B}$<0.001^{X}
				P$^{B/C}$ 0.266^{X}
Birthweight, g	3,336 ± 737	3,252 ± 845	3,239 ± 842	0.484^{A}
Arterial pH (umbilical cord)	7.23 ± 0.09	7.23 ± 0.08	7.23 ± 0.10	0.947^{A}
APGAR '10	9.5 ± 1.4	9.5 ± 1.4	9.6 ± 0.8	0.841^{A}
Atony	366 (69.1%)	39 (76.5%)	65 (76.5%)	0.239^{X}
Placenta adhaerens	215 (40.6%)	18 (35.3%)	44 (51.8%)	0.096^{X}
Obstetric injury	44 (8.3%)	3 (5.9%)	13 (15.3%)	0.081^{X}
Placenta previa	10 (1.9%)	10 (19.6%)	9 (10.6%)	**<0.001**^{X}
				P$^{A/C}$<0.001^{X}
				P$^{A/B}$<0.001^{X}
				P$^{B/C}$ 0.142^{X}

Values are given in absolute number and percentage, as arithmetic mean ± standard deviation and range or as median with interquartile range. In the right column you see the general p-value, when the value was significant ($p < 0.05$) each group was tested with every other group. Statistical tests used: A = ANOVA with Tukey post-hoc, t = independent-sample t-test, KW = Kruskal–Wallis test, X = Chi-squared test. Bold values are significant results.

be hypothesized, that, especially in cases with high risk for PPH, like placenta previa and bleeding from the lower uterine segment, early application of CHT might prevent blood loss and thus morbidity. These findings are in line with Schmid's suggestion of an early use of CHT in high risk situations [9]. This is the first study to provide this data, more research therefore seems justified.

It is very important that there were no differences in secondary outcomes between CHT and BT. In particular, no signs of sepsis, postpartum fever, increased infections or inflammation levels in group C. This could be related to the antibacterial effect of chitosan [29–31]. In other studies, up to 19% of the patients treated with CHT developed low grade fever, but also without clinical signs of infection [8, 32].

Further, no relevant adverse events occurred in relation to the CHT during the follow-up-period of 1–3 years and at least three uncomplicated subsequent pregnancies were documented.

In two reported cases though, retained material had to be removed 6 weeks and 3 months after application [9]. Therefore, we recommend an easy to identify and clear to see label on the patient until removal of the CHT after a maximum of 24 h. Further, we propose the application of a sutured stich at the end of the tamponade to make complete removal obvious and an ultrasound examination of the uterus after removal. CHT appears as a hyperechogenic structure with a dorsal acoustic shadow [10, 28].

Limitations

The study's main limitation is that it is retrospective and thus not randomized. The decision about when and which tamponade was used was individually made by the senior obstetrician on call, which carries the risk of selection bias. However, no relevant differences in patients' demographics of the two tamponade groups were found.

Table 3: Logistic regression analysis adjusted for blood loss in ml and other significant confounders from univariate analysis for the primary outcome (step IV), two of its subitems (sutures, (re-)laparotomy) and two secondary outcomes (admission to Intensive Care Unit, General Anesthesia).

	Odds ratio	95%-CI	p-Values
Step IV adjusted for blood loss, age and mode of birth			
C (chitosan, n=8, 9.4%)	1		
A (medical only, n=18, 3.4%)	2.208	0.724–6.732	0.164
B (balloon, n=8, 15.7%)	1.044	0.274–3.981	0.950
Sutures adjusted for blood loss, age and mode of birth			
C (chitosan, n=5, 6.0%)	1		
A (medical only, n=8, 1.5%)	0.826	0.252–2.701	0.752
B (balloon, n=5/9.8%)	0.819	0.201–3.331	0.780
(Re-) laparotomy adjusted for blood loss, age and mode of birth			
C (chitosan, n=2, 2.4%)	1		
A (medical only, n=6, 1.1%)	6.627	0.661–66.488	0.108
B (balloon, n=4, 7.8%)	2.666	0.231–30.779	0.432
ICU admission adjusted for blood loss, age and mode of birth			
C (chitosan, n=37, 43.5%)	1		
A (medical only, n=27, 5.1%)	0.367	0.205–0.656	**<0.001**
B (balloon, n=30, 58.8%)	0.188	0.255–1.307	0.188

ICU, intensive care unit; 95%-CI, 95% confidence interval. The number of patients with the respective outcome in the different groups is given in absolute numbers and percentages. Odds ratios (OR) are given for the risk of the outcomes to happen in the medical therapy group or the balloon tamponade group in comparison to the chitosan tamponade group with 95% confidence interval (95%-CI) and p-value. Significant results are bold.

Table 4: Univariate analysis of primary (subitems) and secondary outcomes between group B and C.

	B (balloon tamponade)	C (chitosan tamponade)	p-Value
Hysterectomy	4 (7.8%)	0 (0%)	**0.018**^{F}
Embolization	1 (2%)	1 (1.2%)	1.000^{F}
Antibiotic administration	49 (96.1%)	85 (100%)	0.067^{X}
Lowest hemoglobin	4.2 g/dL	4.2 g/dL	
Drop in hemoglobin	4.5 ± 2.01 g/dL	4.74 ± 1.7 g/dL	0.170^{t}
Blood transfusion (1U=400 mL)	1.76 ± 3.08	1.35 ± 2.18	0.397^{t}
FFP (1U=200 mL)	1.96 ± 3.81	1.36 ± 3.02	0.342^{t}
CRP	85.41 ± 81.83 mg/L	102.25 ± 78.63 mg/L	0.420^{t}
Leukocytes	16.74 ± 4.93 G/L	16.37 ± 4.12 G/L	0.657^{t}
Inpatient days	4.73 ± 3.04	4.75 ± 3.01	0.966^{t}

FFP, fresh frozen plasma; CRP, c-reactive protein; U, unit. Values are given in absolute number and percentage or as arithmetic mean ± standard deviation and range. Statistical tests used: t = independent-sample t-test, X = Chi-squared test, F = Fishers exact test. Bold values are significant results.

The fact that the collection device was only placed when increased bleeding became apparent might have led to an underestimation of PPH cases. Further it should also be mentioned that 78 of the 136 cases of uterine packing have already been analyzed in a previous paper [10], scientific approach, study design and outcomes were different, though.

Demographic differences between the groups can be explained by looking at the risk factors for severe PPH and the severity of PPH in the different groups, which was higher in group B and C and lower in group A. Severe PPH is more likely to occur after CS and in cases of placenta previa [33], as well as in certain constellations that more frequently affect older patients. One could argue, that is not reasonable to

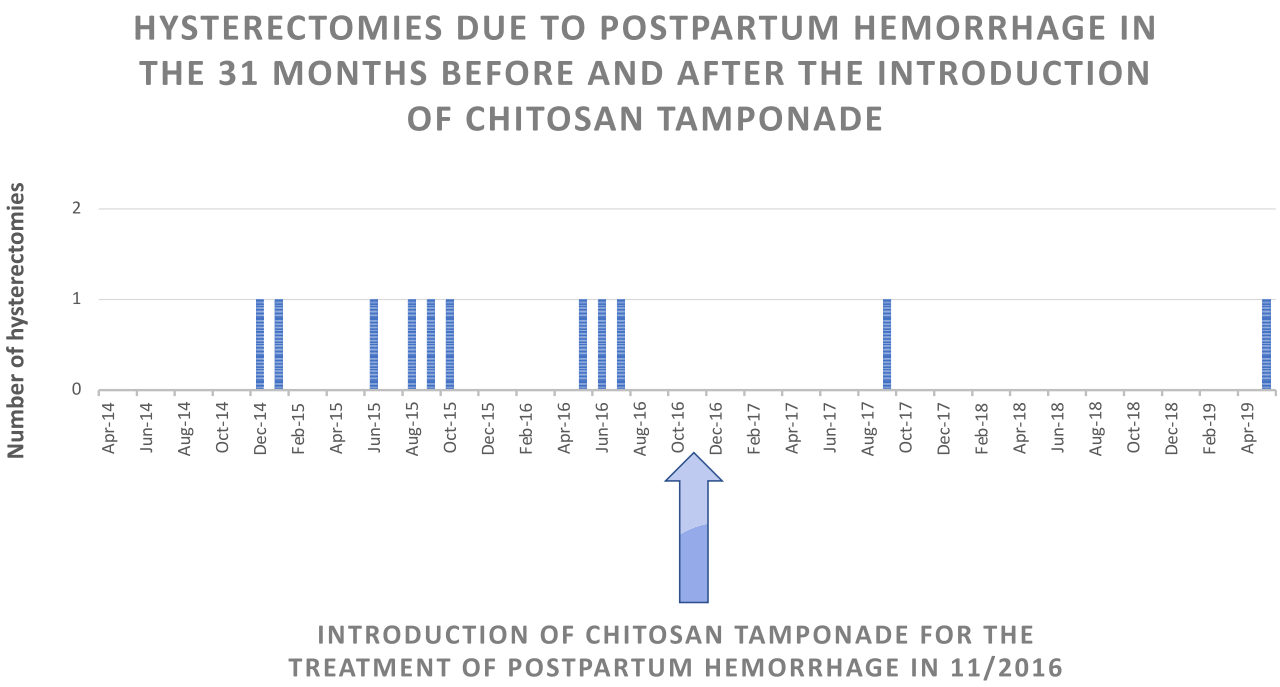

Figure 3: Hysterectomies due to postpartum hemorrhage.

compare group A with the other two groups, considering that they are indicated in different steps of the therapy algorithm. However, confounders such as blood loss and mode of birth were identified and adjusted for and there were also cases of severe PPH in group A who might have had a benefit from uterine packing.

Randomized controlled trials on PPH treatment with higher case numbers are needed to generate more reliable data and to prove if CHT should be implemented into routine practice. Until then we have to rely on historical analysis, and this is the largest historical cohort study on CHT in the treatment of PPH so far.

Conclusions

Chitosan covered gauze is a promising treatment option for PPH. We observed a significant reduction of the HE-rate after its implementation and so far, no side-effects were noted. It might be superior to the balloon tamponade in effectiveness und application. The early use in patients with high risk for bleeding seems justified. It is easy to use and, compared to other devices, inexpensive.

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Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was performed in line with the principles of the Declaration of Helsinki. It was approved by the local Institutional Review Board.

References

1. Diagnosis and management of postpartum hemorrhage. ACOG technical bulletin number 143. Int J Gynaecol Obstet. 1991;36:159–63.
2. Schlembach D, Helmer H, Henrich W, von Heymann C, Kainer F, Korte W, et al. Peripartum haemorrhage, diagnosis and therapy. Guideline of the DGGG, OEGGG and SGGG (S2k level, AWMF registry no. 015/063, March 2016). Geburtshilfe Frauenheilkd 2018;78:382–99.
3. Sentilhes L, Merlot B, Madar H, Sztark F, Brun S, Deneux-Tharaux C. Postpartum haemorrhage: prevention and treatment. Expet Rev Hematol 2016;9:1043–61.
4. Kaya B, Tuten A, Daglar K, Misirlioglu M, Polat M, Yildirim Y, et al. Balloon tamponade for the management of postpartum uterine hemorrhage. J Perinat Med 2014;42:745–53.
5. Wang D, Xu S, Qiu X, Zhu C, Li Z, Wang Z, et al. Early usage of Bakri postpartum balloon in the management of postpartum hemorrhage: a large prospective, observational multicenter

clinical study in South China. J Perinat Med 2018;46: 649–56.
6. Said Ali A, Faraag E, Mohammed M, Elmarghany Z, Helaly M, Gadallah A, et al. The safety and effectiveness of Bakri balloon in the management of postpartum hemorrhage: a systematic review. J Matern Fetal Neonatal Med 2021;34:300–7.
7. Schmid BC, Rezniczek GA, Rolf N, Maul H. Postpartum hemorrhage: use of hemostatic combat gauze. Am J Obstet Gynecol 2012;206:e12–3.
8. Von Beckerath AK, Maul H, Gebauer G, Abdel-Kawi AF, Rolf N, Saade G, et al. 492: use of chitosan-covered gauze (Celox) in 98 cases of severe postpartum hemorrhage – a multicenter registry analysis. Am J Obstet Gynecol 2016;214:S269.
9. Schmid BC, Rezniczek GA, Rolf N, Saade G, Gebauer G, Maul H. Uterine packing with chitosan-covered gauze for control of postpartum hemorrhage. Am J Obstet Gynecol 2013;209:225.e1–5.
10. Dueckelmann AM, Hinkson L, Nonnenmacher A, Siedentopf JP, Schoenborn I, Weizsaecker K, et al. Uterine packing with chitosan-covered gauze compared to balloon tamponade for managing postpartum hemorrhage. Eur J Obstet Gynecol Reprod Biol 2019;240:151–5.
11. Carles G, Dabiri C, McHirgui A, Saoudi EO, Hcini N, Pouget K, et al. Uses of chitosan for treating different forms of serious obstetrics hemorrhages. J Gynecol Obstet Hum Reprod 2017;46:693–5.
12. Available from: https://www.celoxmedical.com/ [Accessed 7 May 2022].
13. Muzzarelli RAA. Biochemical significance of exogenous chitins and chitosans in animals and patients. Carbohydr Polym 1993;20:7–16.
14. Klokkevold PR, Fukayama H, Sung EC, Bertolami CN. The effect of chitosan (poly-N-acetyl glucosamine) on lingual hemostasis in heparinized rabbits. J Oral Maxillofac Surg 1999;57:49–52.
15. Waibel KH, Haney B, Moore M, Whisman B, Gomez R. Safety of chitosan bandages in shellfish allergic patients. Mil Med 2011; 176:1153–6.
16. Bamberg C, Niepraschk-Von Dollen K, Mickley L, Henkelmann A, Hinkson L, Kaufner L, et al. Evaluation of measured postpartum blood loss after vaginal delivery using a collector bag in relation to postpartum hemorrhage management strategies: a prospective observational study. J Perinat Med 2016;44:433–9.
17. Schlembach D, Mörtl MG, Girard T, Arzt W, Beinder E, Brezinka C, et al. [Management of postpartum hemorrhage (PPH): algorithm of the interdisciplinary D-A-CH consensus group PPH (Germany–Austria–Switzerland)]. Anaesthesist 2014;63:234–42.
18. Available from: https://www.cookmedical.com/products/wh_sosr_webds/ [Accessed 7 May 2022].
19. Moleiro ML, Braga J, Machado MJ, Guedes-Martins L. Uterine compression sutures in controlling postpartum haemorrhage: a narrative review. Acta Med Port 2022;35:51–8.
20. Seidel V, Braun T, Chekerov R, Nonnenmacher A, Siedentopf JP, Henrich W. Vaginal omentum prolapse due to uterine anterior wall necrosis after compression suture for postpartum hemorrhage (PPH): case report and Review of the literature. Case Rep Perinat Med 2017;6:1–12.
21. Collins SL, Alemdar B, van Beekhuizen HJ, Bertholdt C, Braun T, Calda P, et al. Evidence-based guidelines for the management of abnormally invasive placenta: recommendations from the international society for abnormally invasive placenta. Am J Obstet Gynecol 2019;220:511–26.
22. Shields LE, Goffman D, Caughey AB. Practice bulletin no. 183: postpartum hemorrhage. Obstet Gynecol 2017;130:e168–86.
23. Surbek D, Irion O, Hess T, Drack G. [Current treatment options in postpartum hemorrhage. Expert correspondence no. 26 of 26 May 2009]. Gynäkol-Geburtshilfliche Rundsch 2009;49:337–40.
24. Dahlke JD, Mendez-Figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. Am J Obstet Gynecol 2015;213:76.e1–10.
25. Suarez S, Conde-Agudelo A, Borovac-Pinheiro A, Suarez-Rebling D, Eckardt M, Theron G, et al. Uterine balloon tamponade for the treatment of postpartum hemorrhage: a systematic review and meta-analysis. Am J Obstet Gynecol 2020;222:293.e1–52.
26. Belfort MA, Dildy GA, Garrido J, White GL. Intraluminal pressure in a uterine tamponade balloon is curvilinearly related to the volume of fluid infused. Am J Perinatol 2011;28:659–66.
27. Wright CE, Chauhan SP, Abuhamad AZ. Bakri balloon in the management of postpartum hemorrhage: a review. Am J Perinatol 2014;31:957–64.
28. Seidel V, Braun T, Weizsäcker K, Henrich W. Application of chitosan-covered gauze in combination with intrauterine balloon tamponade for postpartum hemorrhage treatment – case report of a novel “uterine sandwich” approach. Int J Surg Case Rep 2018; 48:101–3.
29. Tsai GJ, Su WH. Antibacterial activity of shrimp chitosan against Escherichia coli. J Food Protect 1999;62:239–43.
30. Suzuki K, Shinya M, Kitagawa M. Basic study of healing of injuries to the myometrium and amniotic membrane using photocrosslinkable chitosan. J Obstet Gynaecol Res 2006;32: 140–7.
31. Matica MA, Aachmann FL, Tøndervik A, Sletta H, Ostafe V. Chitosan as a wound dressing starting material: antimicrobial properties and mode of action. Int J Mol Sci 2019;20. https://doi.org/10.3390/ijms20235889.
32. Von Beckerath AK, Maul H, Elmohandes AM, Shaaban M, Habib DM, Nasr A, et al. 628: comparison of Celox and Bakri balloon in management of primary atonic postpartum hemorrhage. Am J Obstet Gynecol 2016;214:S335.
33. Nyfløt LT, Sandven I, Stray-Pedersen B, Pettersen S, Al-Zirqi I, Rosenberg M, et al. Risk factors for severe postpartum hemorrhage: a case-control study. BMC Pregnancy Childbirth 2017;17:17.