Outcome of Surgical Interventions and Deliveries in Patients with Bleeding of Unknown Cause: An Observational Study

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Abstract

Background The most optimal management for patients with bleeding of unknown cause (BUC) is unknown, as limited data are available.

Objective Evaluate management and outcome of surgical procedures and deliveries in patients with BUC.

Materials and Methods All patients ≥12 years of age, referred to a tertiary center for a bleeding tendency, were included. Bleeding phenotype was assessed and hemostatic laboratory work-up was performed. Patients were diagnosed with BUC or an established bleeding disorder (BD). Data on bleeding and treatment during surgical procedures and delivery following diagnosis were collected.

Results Of 380 included patients, 228 (60%) were diagnosed with BUC and 152 (40%) with an established BD. In 14/72 (19%) surgical procedures major bleeding occurred and 14/41 (34%) deliveries were complicated by major postpartum hemorrhage (PPH). More specifically, 29/53 (55%) of the BUC patients who underwent surgery received prophylactic treatment to support hemostasis. Despite these precautions, 4/29 (14%) experienced major bleeding. Of BUC patients not treated prophylactically, bleeding occurred in 6/24 (25%). Of pregnant women with BUC, 2/26 (8%) received prophylactic treatment during delivery, one women with and 11 (46%) women without treatment developed major PPH.

Conclusion Bleeding complications are frequent in BUC patients, irrespective of pre- or perioperative hemostatic treatment. We recommend a low-threshold approach toward administration of hemostatic treatment in BUC patients, especially during delivery.

Keywords
- hemostasis
- bleeding of unknown cause
- von Willebrand disease

Introduction

Patients with easy bruising, mucosal bleeding, menorrhagia, and disproportionate bleeding after minor injuries, trauma, and surgery are frequently referred to a hematologist to diagnose or to rule out an inherited bleeding disorder (BD).[1] Diagnoses in these patients vary and consist of primary hemostasis disorders, e.g., von Willebrand disease and platelet disorders, or secondary hemostasis disorders, e.g., hemophilia or other rare coagulation factor deficiencies, or

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disorders of fibrinolysis and collagen disorders. However, in approximately 50% of these referred patients laboratory tests are normal even after extensive testing.[1–4] These patients are diagnosed with bleeding of unknown cause (BUC). The lack of a clear cause of bleeding often leads to uncertainty and insecurity for patients and treating physicians with regard to therapeutic management in the case of hemostatic challenges such as dental or surgical procedures, trauma, or childbirth, as only limited evidence on most effective treatment is available.[5] As a consequence, these patients are regularly under-treated or over-treated, respectively, leading to increased bleeding (risk) or excessive costs.

To our knowledge, only two studies have documented the characteristics and clinical management of BUC patients during therapeutic interventions. Both studies demonstrated that effective prevention or cessation of bleeding occurred in 90% of BUC patients treated with desmopressin and/or tranexamic acid (TXA).[5,6] However, we believe that increased insight into this patient group will lead to better tailoring of treatment strategies. Therefore, in a large cohort study, we retrospectively identified patients referred to a tertiary clinic for hemostatic evaluation and diagnosed with either BUC, a mild BD, or an established BD. Subsequently, outcomes of surgical procedures and deliveries were evaluated.

Methods

Study Population

All consecutive patients, aged 12 years and older, referred to the outpatient hematology clinics of the Erasmus University Medical Centre and/or the Erasmus University Medical Centre—Sophia Children's Hospital between 2014 and 2018 for hemostatic screening due to a bleeding tendency or an affected family member with a BD, were included in this study. Patients previously diagnosed with a BD were excluded. Medical records of all included patients, until a year after the last inclusion, were analyzed and follow-up data regarding surgical procedures and deliveries occurring after referral for hemostatic evaluation were collected. Of all the included patients, at least a 1 year follow-up period was available. This study was not subject to the Medical Research Involving Human Subjects Act and approved by the Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam.

Bleeding Assessment Tools

The Condensed MCMDM-1 VWD (Molecular and Clinical Markers for the Diagnosis and Management of Type 1 Von Willebrand disease) bleeding questionnaire or the ISTH-BAT (International Society of Thrombosis and Hemostasis Bleeding Assessment Tool) was used by the (pediatric) hematologist to evaluate bleeding symptoms. The cut-off value for an abnormal score using the Condensed MCMDM-1 VWD bleeding questionnaire is $\geq$4 for all ages and sex.[7] For the ISTH-BAT, cut-off values for an abnormal score are $\geq$4 in male adults, $\geq$6 in female adults, and $\geq$3 in children under 18 years of age.[8]

Blood Sampling Procedure and Laboratory Assays

Blood sampling was performed using a Vacutainer system (Becton Dickinson) and vials containing either sodium citrate (final concentration 0.109 mol/L) or EDTA (1.8 mg/mL, Plymouth). Blood cell count and blood type were determined. Routine coagulation tests, activated partial thromboplastin time (aPTT; Actin FS), prothrombin time (Thromborel S), and fibrinogen (Thrombin Reagent), were measured on a Sysmex CS5100 (Siemens Healthcare Diagnostics B.V.). Collagen-ADP and collagen-epinephrine cartridges were used to measure closure times (seconds) on the PFA-200 (Siemens). Light transmission aggregometry was performed on a Chrono-Log aggregometer 490 (Stago Benelux B.V.). Von Willebrand factor antigen (VWF:Ag) levels were determined with an in-house enzyme-linked immunosorbent assay (ELISA) assay, using polyclonal rabbit antihuman VWF antibodies (DakoCytomation) for capturing and detection. VWF collagen-binding (VWF:CB) activity was measured by an in-house ELISA assay using bovine Achilles tendon collagen type I for capturing (Sigma-Aldrich) and polyclonal rabbit antihuman VWF antibodies (DakoCytomation) for detecting. VWF activity (VWF:GPIbM) was determined with the INNOVANCE VWF Ac assay (Siemens) on a Sysmex CS5100. Factor (F)VIII and FIX coagulant activities (FVIII:C/FIX:C) were measured using one-stage clotting assays and derived from (the prolongation of) the clotting time (aPTT) measured on the Sysmex CS-5100 (Siemens). FXIII activity was measured using the Berichrom FXIII kit (Siemens) on the Sysmex CS5100 (Siemens). Alpha 2-antiplasmin was measured using a chromogenic assay (Stachrom, Stago) on the Sysmex CS5100 (Siemens).

Categorization of Diagnoses

Based on medical history and laboratory investigation, patients were divided into two diagnostic categories:

- BUC: bleeding was considered of unknown cause based on a clinically relevant bleeding history but no detection of hemostatic abnormalities after extensive laboratory investigation, as described before.[5,9,10]
- Established BD: a BD was confirmed if the identified laboratory abnormalities were in accordance with the definitions of an established BD (e.g., von Willebrand disease or hemophilia) stated in national and international guidelines.[11–15]

Definitions of Low-, Moderate-, and High-Risk Surgical Procedures and Bleeding Complications

Definitions of low-, moderate-, and high-risk surgical procedures were defined as described before (►**Supplementary Table S1a**, available in the online version).[16] Definitions of major bleeding, clinically relevant minor bleeding, and (major) postpartum hemorrhage (PPH) are as stated by the ISTH[17,18] and World Health Organization[19] (►**Supplementary Table S1b**, available in the online version). In the case of PPH, the amount of blood loss was visually estimated until a blood loss of 500 mL. In the case of more than 500 mL blood loss, the amount was estimated by measuring the volume of the blood lost and by weighing the drapes, as routinely is performed.

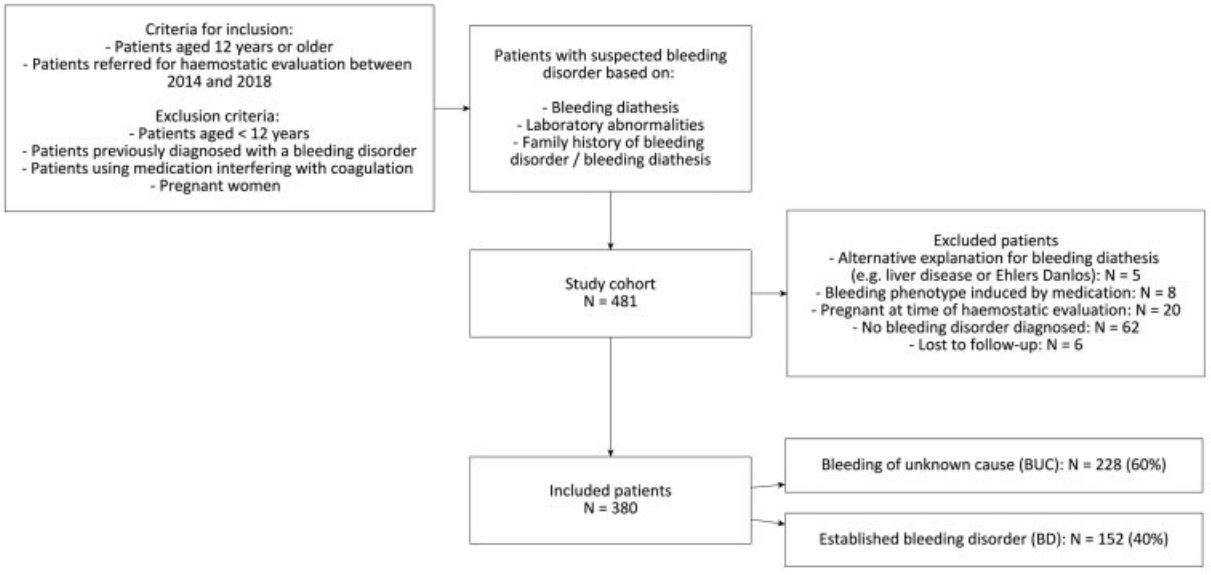

Fig. 1 Flowchart of inclusion.

Statistics

We used descriptive statistics to summarize baseline characteristics of all patient groups. In case of a skewed distribution, data are presented as median and interquartile range (IQR). Categorical data are presented as numbers with percentages. All analyses were performed with SPSS version 21.0 (IBM, Armonk, New York, United States).

Results

Study Group Characteristics

Between 2014 and 2018, 481 patients referred for hemostatic evaluation were eligible for inclusion. In total, 101 patients were excluded for various reasons: six patients were lost to follow-up, five patients had a liver disease or Ehlers–Danlos syndrome, eight patients used medication that interfered with hemostasis, and 20 women were pregnant at the time of hemostatic evaluation. Sixty-two patients were classified as having no BD, based on no bleeding history as judged by the hematologist and normal laboratory results. After exclusion of these patients, a total of 380 patients with a bleeding phenotype remained, of whom 228/380 (60%) were classified as having BUC and 152/380 (40%) had an established BD (►**Fig. 1**). The median age was 32 years (IQR: 20–47 years), and 79% were females, with the highest percentage of women found in patients with BUC. Blood type O was present in 53% of patients, and 45% of patients had an abnormal bleeding score (BS) at the time of hemostatic evaluation, with the highest percentage of both blood type O and abnormal BSs found in patients with a BD (►**Table 1**).

Of the patients with a diagnosed BD, 25 patients were diagnosed with VWD and 43 patients had a mild VWD type 1. Five patients were diagnosed with hemophilia and 12 patients were diagnosed as hemophilia carriers. Other factor deficiencies (FVII and FXI deficiencies) were found in 18 patients. A total of 45 patients had a platelet function disorder, and four patients had a hypo- or dysfibrinogenemia.

Surgical Procedures Complicated by Major Bleeding

During this study, 72 surgical procedures were performed in 66 patients (►**Table 2**). In the total study cohort, 19% of surgical procedures were complicated by major bleeding (►**Fig. 2**).

For BUC patients, 29/53 patients received prophylactic hemostatic treatment. In total, 10/53 (19%) of surgical procedures were complicated by major bleeding. Of the patients receiving treatment, 4/29 (14%) of procedures were complicated by major bleeding. Of the patients receiving no treatment, 6/24 (25%) of procedures were complicated by major bleeding. Of the BUC patients receiving treatment, 27 patients received TXA with or without desmopressin. One patient received a platelet transfusion, and one patient received solely clotting FVIII/VWF concentrate. For BD patients receiving prophylactic treatment (15/19), 3/15 (20%) of procedures were complicated by major bleeding; of the 4/19 patients receiving no treatment, one suffered major bleeding. No statistical significant differences were found between major bleedings in patients with or without hemostatic treatment (►**Fig. 3**). Detailed information about surgical procedures, treatment, and outcome in patients with BUC can be found in ►**Supplementary Tables 2** and **3** (available in the online version).

Low-, Moderate-, and High-Risk Surgical Procedures and Major Bleeding

Of the 72 surgical procedures, seven procedures were classified as having a high bleeding risk, 36 procedures as having a moderate bleeding risk, and 29 procedures as having a low bleeding risk surgical procedure. Four of the seven patients with a high-risk procedure received prophylactic hemostatic therapy, of which one procedure was complicated by major bleeding. Of the patients with moderate-risk procedures, 21/36 (58%) received prophylactic hemostatic treatment, of which five procedures (24%) were complicated by major bleeding. Of the patients with low-risk procedures, 18/29 (62%) received prophylactic hemostatic treatment. One low-risk procedure was

Table 1 Study group characteristics

	Total	BUC	BD
No of patients, *n* (%)	380 (100%)	228 (60%)	152 (40%)
Age, median [IQR]	32 [20–47]	33 [23–48]	29 [19–47]
Female, *n* (%)	300 (79%)	186 (82%)	114 (75%)
Blood group O, *n* (%)[a]	146 (53%)	81 (48%)	65 (60%)
Positive family history	95 (25%)	33 (14%)	60 (39%)
Reason for referral			
Bleeding symptoms	290 (76%)	212 (93%)	78 (51%)
Family history	55 (14%)	10 (4%)	45 (30%)
Other	35 (9%)	6 (3%)	29 (19%)
Abnormal bleeding score, *n* (%)[a]	145 (45%)	89 (45%)	56 (46%)
VWF levels, U/mL			
VWF:Ag, median [IQR]	0.90 [0.66–1.28]	1.01 [0.76–1.39]	0.71 [0.49–1.11]
VWF:Act, median [IQR]	0.85 [0.64–1.22]	0.96 [0.76–1.36]	0.64 [0.41–0.98]
VWF:CB, median [IQR]	0.91 [0.65–1.28]	1.05 [0.81–1.43]	0.71 [0.45–0.99]
FVIII:C levels (U/mL), median [IQR]	1.16 [0.90–1.44]	1.23 [1.08–1.62]	0.94 [0.66–1.21]

Abbreviations: Act, activity; Ag, antigen; BD, bleeding disorder; BUC, bleeding of unknown cause; CB, collagen binding; FVIII:C, factor VIII activity; VWF, von Willebrand factor.
[a]Based on available data.

Table 2 Number and characteristics of surgical procedures per patient group

	BUC	BD
No. of surgical procedures	60	25
Type of surgical procedure[16]		
High bleeding risk	9	4
Moderate bleeding risk	28	9
Low bleeding risk	23	12
Data complete (treatment and outcome)	53	18
Treatment		
None	25	4
TXA alone	8	1
Desmopressin ± TXA	18	8
Clotting factor concentrate ± TXA	1	4
Platelet transfusion ± TXA	–	1
Desmopressin + platelet transfusion ± TXA	1	–

Abbreviations: BUC, bleeding of unknown cause; BD, bleeding disorder; TXA, tranexamic acid.

complicated by major bleeding (6%) (►**Supplementary Fig. S1**, available in the online version).

Deliveries Complicated by Major PPH

A total of 43 deliveries in 40 women were registered during the study period, of whom 32/43 (74%) were vaginal deliveries. Based on available data about management and outcome of deliveries following hemostatic evaluation ($n = 41$), 14/41 (34%) of deliveries was complicated by major PPH. In total, 16/43 (37%) of women had major PPH in their medical history at the time of hemostatic evaluation. Of these 16 women, 11/16 (69%) had major PPH at a subsequent delivery during the follow-up period. The patient category with the highest percentage of major PPH was BUC, with 12/26 (46%) of all deliveries being complicated by major PPH. Of these BUC women, only 2/26 (8%) received treatment, being solely TXA, with 1/2 deliveries being complicated by major PPH. In BD patients, 7/15 women were treated before delivery, with 2/7 delivery being complicated by major PPH. No statistical significant differences were found between major PPHs in women who received hemostatic treatment and women who did not receive hemostatic treatment during delivery (►**Fig. 3**). For detailed information about the number of deliveries, treatment per patient category, and obstetric risk factors, see ►**Table 3**. Detailed information about surgical procedures, treatment, and outcome in patients with BUC can be found in ►**Supplementary Tables 2**, **3**, and **4a**, **b** (available in the online version).

Bleeding Score, Treatment, and Major Bleeding

Significantly more patients with an abnormal BS received perioperative or peripartum treatment (28/47, 60%) compared with patients with a normal BS (19/53, 36%, $p = 0.018$) upon hemostatic evaluation.

Of all the patients with a major bleeding during follow-up (including major PPH) of whom a BS was calculated by the treating physician at the time of diagnosis ($n = 27$), 9/27 (33%) had an abnormal BS. Of the patients with a major bleeding during surgery of whom a BS was obtained ($n = 14$), 4/14 (29%) had an abnormal BS. Of all the women with major

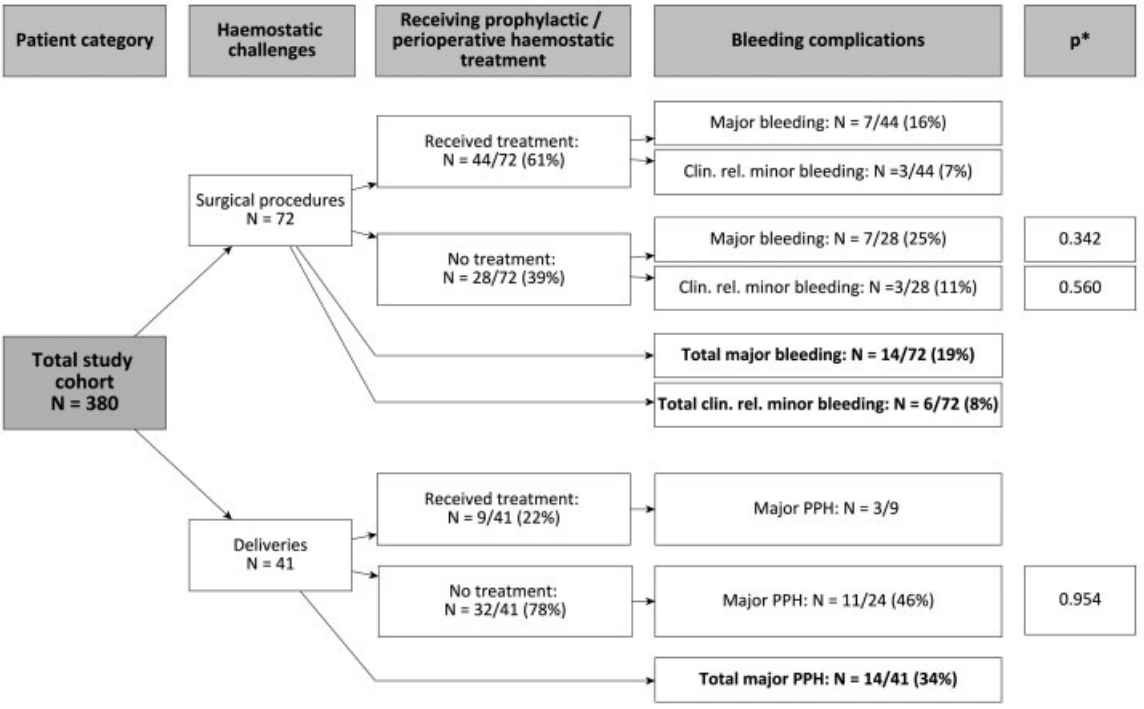

Fig. 2 Flowchart of surgical procedures and deliveries (total study cohort).

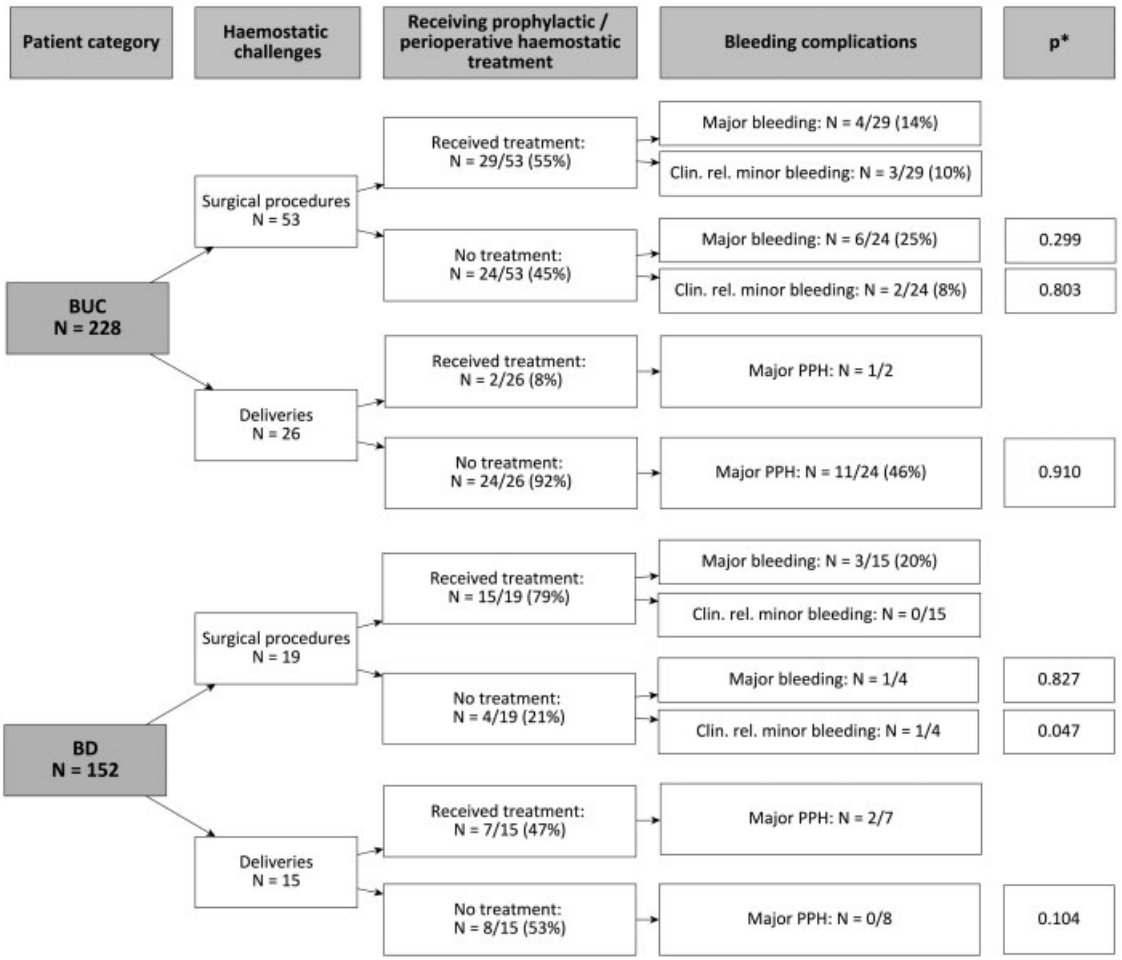

Fig. 3 Flowchart of surgical procedures and deliveries (diagnostic subgroups).

Table 3 Number and characteristics of deliveries per patient group

	BUC	BD
No. of deliveries	27	16
Vaginal	20	12
Caesarian section	7	4
Major PPH in medical history	11 (42%)	5 (31%)
Data complete (treatment and outcome)	26	15
Treatment		
None	24	8
TXA alone	2	–
Desmopressin ± TXA	–	2
Clotting factor concentrate ± TXA	–	4
Platelet transfusion ± TXA	–	1
Present peri- and/or postpartum obstetric risk factors for PPH		
Atonic uterus	2	1
Retained placenta	5	–
Rupture of any kind	12	4
Coagulopathy/preeclampsia	1	–
Placental abnormalities	3	–

Abbreviations: BUC, bleeding of unknown cause; BD, bleeding disorder; PPH, postpartum hemorrhage; TXA, tranexamic acid.

PPH of whom a BS was available ($n = 13$), 5/13 (38%) had an abnormal BS.

Of the patients who had a surgical procedure during follow-up and scored 1 or higher on the BAT item surgical bleeding ($n = 38$) at the time of hemostatic evaluation, indicating previous bleeding during surgery, 8/38 (21%) had a major bleed, versus 6/23 (26%) patients without previous surgical bleeding (BS < 1, $n = 23$) ($p = 0.650$). Of the women who gave childbirth during follow-up and had a score of 1 or higher on the BAT item PPH ($n = 15$) at the time of hemostatic evaluation, indicating PPH in their medical history, 11/15 (73%) had major PPH on follow-up, versus 2/22 (9%) in women without previous PPH (BS < 1, $n = 22$) ($p < 0.01$).

Regression analysis showed no association between outcomes of surgery and delivery and total BS, corrected for received treatment, with an odds ratio (OR) of 1.02 (95% confidence interval [CI]: 0.90–1.16) for all complications combined (major bleeding, clinically relevant minor bleeding, major PPH, and PPH), an OR of 0.94 (95% CI: 0.81–1.09) for major bleeding (including major PPH), and an OR of 1.15 (95% CI: 0.97–1.36) for clinically relevant minor bleeding (including PPH).

Discussion

This study reports on a cohort of 380 patients referred for analysis of a bleeding tendency to a tertiary outpatient clinic. Sixty percent of these patients were classified as BUC. Of the surgical procedures performed in this patient group, 19% were complicated by a major bleed and 46% of the deliveries were complicated by major PPH.

In our study, of the 53 surgical procedures performed in the BUC patient group, 55% of patients received treatment before surgery. In the patients receiving hemostatic therapy, 14% of surgical procedures were complicated by major bleeding and 10% by clinically relevant minor bleeding, indicating that more than 75% of patients experienced no complications during surgery. This is in line with the results obtained by Obaji et al[5] and MacDonald et al,[6] the two studies that have investigated surgical outcome in a large group of patients with BUC. In these studies, hemostatic therapy, consisting of desmopressin and/or TXA, was administered in almost all BUC patients, with effective hemostasis in 90% of cases. Major bleeding in 19% of patients after surgery in our total study population, as well as in BUC patients, is however much higher than that found in the general population. Normally, postsurgical bleeding ranges from 0.6% in orthopaedic procedures[20] to around 3% after tonsillectomy in healthy adults.[21] Furthermore, a large prospective international cohort study of outcomes following elective inpatient surgery in over 44,000 patients showed that 3% of procedures are complicated by postoperative bleeding, with 0.5% major bleeding.[22] Also, in a study by Mauer et al,[23] peri- and postsurgical bleedings were reported in only 6% of included healthy adults. Therefore, we conclude that BUC patients have a higher risk of bleeding compared with the general population.

A striking finding was the occurrence of PPH in nearly half of the women during childbirth after being analyzed for a bleeding tendency, with one-third of deliveries being complicated by major PPH. Of the women with major PPH, the majority had a medical history of major PPH and thus seem to be at higher risk of recurrent PPH. It is known that a history of PPH gives a threefold higher chance of recurrence during subsequent deliveries.[24,25] Also, Stoof et al[26] previously reported that even in patients with an established BD (VWD or hemophilia carriers) receiving prophylactic hemostatic treatment during delivery, still 34% of women present with PPH.

Of the women with BUC, only 8% received hemostatic treatment pre- or peripartum. A total of 46% of women with BUC, however, experienced major PPH after hemostatic evaluation. This percentage is over 10 times higher than the incidence of major primary PPH in the general Dutch population (4.5%).[27] In a recently published international, randomized, placebo-controlled trial (WOMAN trial), it was found that TXA reduces death due to bleeding in women with PPH without adverse effects.[28] When used as treatment for PPH, it is recommended to give TXA as soon as possible after bleeding onset. Momentarily, the WOMEN II trial is open aiming to establish if prophylactic TXA in high-risk women with regard to bleeding is protective.

Because no laboratory abnormalities are identified in patients with BUC, the pathogenesis of the bleeding phenotype remains unknown. Theoretically, bleeding may be

caused by a higher fibrinolytic activity, or may be multifactorial, and caused by several subtle impairments of primary hemostasis and/or secondary hemostasis, together leading to impaired clot formation. This may explain why bleeding is often controlled effectively by medication that does not compensate for one deficient factor such as desmopressin and TXA, which have been reported to reduce blood loss and transfusion requirements without thrombotic adverse effects found in several placebo-controlled studies.[28–31]

A recently published consensus report by the European Hematology Association[32] states that the aim of a BAT is not to demonstrate a strict correlation between any identifiable BD and BS calculated based on a BAT, but to identify those individuals who may benefit from identification as an individual with a significant risk of future bleeding. This statement is supported by two major studies that show that a high BS is predictive of postsurgical bleeding for patients with various types of VWD[33] and inherited platelet function disorders.[34] Furthermore Relke et al[35] found that a higher BS was associated with a significantly higher risk of future spontaneous bleeding events in BUC patients. Thus, a useful application of BATs could be the ability to identify (BUC) patients who are more likely to bleed excessively during invasive procedures, surgery, and childbirth. Unfortunately, we were not able to confirm this finding as we did not find significant associations between a normal and an abnormal BS, or specific items scored on a BAT with surgical outcome and delivery. This may be explained by the small number of procedures and deliveries in our study. Therefore, larger prospective studies must further investigate the value of a BAT in predicting future bleeding complications during hemostatic challenges. We did once again confirm that a history of PPH is a risk factor for future (major) PPH. Based on our own data, specifically in women with a history of PPH and in BUC patients, extra-awareness for the risk of (recurrent) PPH is needed. A low threshold approach toward bleeding risk during the third stage of delivery with early administration of uterotonics and additional hemostatic therapy, such as TXA, is recommended.

Our study has some limitations. First, our study is a retrospective analysis of real-world data on how patients with a bleeding tendency are treated during hemostatic challenges. Prospective trials are needed to confirm our findings and to further investigate the most optimal management strategy for patients with BUC, as they seem to be at higher risk for bleeding complications following surgery and especially delivery. Second, a possible selection bias could have occurred due to our status of a tertiary center, as some surgical procedures and deliveries were performed or managed in other regional hospitals. This, together with a low sample size of complications, might explain that no significant differences were found between patients receiving and not receiving perioperative treatment. Also, information on pre- or perioperative treatment regimens and outcomes was not available for all patients analyzed at our outpatient clinic.

In conclusion, bleeding complications during surgery are frequent in BUC patients, irrespective of pre- or perioperative hemostatic treatment, compared with the general population. In BUC women major PPH occurred frequently during follow-up and a history of PPH was a major risk factor for future (major) PPH. We recommend a low-threshold approach toward hemostatic treatment especially during delivery in BUC patients.

What is known about this topic?

- Approximately 50% of patients with a bleeding tendency are diagnosed with bleeding of unknown cause (BUC), even after extensive hemostatic evaluation.
- The lack of a clear cause of bleeding often leads to uncertainty and insecurity with regard to therapeutic management in case of hemostatic challenges, such as dental or surgical procedures, trauma, or childbirth.

What does this paper add?

- Bleeding complications during surgery are frequent in BUC patients, irrespective of pre- or perioperative hemostatic treatment.
- In BUC women major PPH occurred frequently during follow-up; a history of PPH was a major risk factor for future (major) PPH.
- No significant associations were found between bleeding scores, or specific items scored on a bleeding assessment tool (BAT), and surgical outcome or postpartum hemorrhage.

Author Contributions

C.S.B.V., E.J.H., M.H.C., F.W.G.L., and M.J.H.A.K. designed the study; C.S.B.V., E.J.H., L.G.R.R., and C.W.A.S. collected the data; C.S.B.V. and C.W.A.S. performed the statistical analyses; C.S.B.V., E.J.H., M.P.M.M., and M.J.H.A.K. interpreted the data; C.S.B.V. and M.J.H.A.K. wrote the manuscript. All authors critically revised the manuscript, agreed with its content, and approved for submission.

Conflict of Interest

None declared.

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