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Retrospective Review of the Management of Elective Surgery With Desmopressin and Clotting Factor Concentrates in Patients With von Willebrand Disease

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Limited data are available regarding optimal treatment with desmopressin (DDAVP) or intermediate-purity FVIII concentrates rich in VWF (CFCs) in patients with von Willebrand disease (VWD) who undergo planned surgery. We undertook a retrospective review over 10 years (1988–1997) and identified 27 patients treated with DDAVP for 35 surgical events and 38 patients who received CFCs for 68 elective surgical events. Tranexamic acid was usually added for mucosal surgery. The FVIII:C levels and the severity of surgery were used to determine the frequency and the doses of postoperative treatment. For major surgery the median pre- and post-operative doses of CFCs were 54 and 43 IU/kg, respectively, and for minor surgery the median doses varied between 34 and 52 IU/kg preoperatively and between 23 and 37 IU/kg postoperatively. The effectiveness of haemostasis was excellent in 32 events (91%) treated with DDAVP and in 56 events (82%) treated with CFCs. It is concluded that patients with VWD do not carry an increased operative risk if appropriate therapy is given. Am. J. Hematol. 66:280–284, 2001.

Key words: von Willebrand disease; surgery; desmopressin; clotting factor concentrates; protocols

INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder caused by quantitative or qualitative defects of von Willebrand factor (VWF), with an estimated prevalence of 1% in the general population [1]. The treatment of patients with VWD undergoing surgery is a challenging task, as the haemostatic response in the face of surgery cannot be accurately predicted. Furthermore, patients with severe VWD who have extensive surgery or surgery involving sites with an increased fibrinolysis, such as oropharyngeal mucosa, digestive tract, or uterus, have a certain increased bleeding risk. Large prospective or retrospective studies about the appropriate prophylactic regimens during surgery are very few, and in general the management of these patients is guided by the type of surgery, the type and severity of VWD, and the choice of treatment. However, there are no clear guidelines on the optimal dosage, the duration of treatment, or the adequate monitoring of these patients [2].

The treatment of VWD consists of two main forms: desmopressin (DDAVP) and clotting factor concentrates (CFCs). Desmopressin is a vasopressin analogue that can increase plasma factor VIII (FVIII) and VWF levels three to five times above baseline [3]. In the responsive patient (usually with type 1 and certain type 2 VWD), DDAVP is the treatment of choice as it has the advantage of being inexpensive and it carries no risk of blood-borne viruses.

CFCs are successfully used for treatment of patients unresponsive to DDAVP or if DDAVP is contraindicated, despite their limited and inconsistent effects on the bleeding time (BT) [4]. The CFCs usually used to treat VWD are plasma-derived intermediate-purity FVIII concentrates rich in VWF. Their therapeutic success in preventing or treating postoperative bleeding is due to the

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high FVIII content, which is the main determinant of postoperative bleeding. However, the adequate dosage is difficult as the content of VWF is not always standardized and varies considerably with different concentrates. However, comparative studies between various CFCs have shown that Haemate P is one of the "golden standard" concentrates as it contains 2.5 IU ristocetin cofactor activity to 1 IU of FVIII:C and has a nearly normal multimeric content (84.1% of the corresponding bands in normal plasma) [5,6]. The content of multimers present in a concentrate is an important characteristic as the high molecular weight forms of the multimers are haemostatically most effective.

Other CFCs used for the treatment of VWD are high-purity VWF products that have a low FVIII content and an almost normal multimeric pattern; recently recombinant human VWF has been developed and it is still under study.

The laboratory monitoring of patients undergoing surgery is a controversial issue. The majority of the treating centres monitor only the FVIII:C levels, as the assay is relatively easy and widely available [7]. However for muco-cutaneous surgery there are reports that the correction of the BT and the contribution of platelet VWF are also important [8].

In this report we undertook a retrospective survey spanning 10 years of experience in the management of planned surgery in patients with VWD registered at a single institution. We analysed the treatment options, the protocols, and the outcomes of haemostasis in the context of surgery, and we compared our experience with the limited data available in the literature.

MATERIALS AND METHODS

Patient Selection

The records of all patients with VWD who underwent a planned surgical event, invasive procedure, or obstetric delivery by Caesarian section between 1988 and 1997 were analysed retrospectively. We identified a total of 65 patients with VWD regularly followed up at our Centre who underwent surgery during the study period. This group of patients underwent 103 surgical procedures that required prophylactic treatment with either desmopressin or CFCs. If a patient underwent more than one similar surgical event that was treated and responded in a similar fashion (in most cases this was a dental procedure), only one entry was made for the respective patient.

CFCs were the treatment of choice in patients with type 2B and type 3 VWD where DDAVP is contraindicated or ineffective. In type 1 and certain type 2 VWD cases, the majority of patients underwent a standard test dose of DDAVP administered intravenously in a dose of 0.3 μg/kg. The patient was considered DDAVP-responsive if within an hour of DDAVP administration the FVIII/VWF levels were normalised (≥50 IU/dl).

One patient with type 3 VWD who underwent a tonsillectomy in 1994 was excluded from this analysis, as his management and response to therapy was unusual. He required 5 weeks of daily treatment and several months of intermittent treatment with Haemate P for severe postoperative bleeding [9].

Type of Surgery

All surgical procedures were performed at the Royal Free Hospital London and were divided into five main groups: major surgery (abdominal, intra-cranial, and orthopaedic surgery), minor surgery (invasive procedures such as arthroscopy, GI endoscopy, cystoscopy, or urethral dilatation or minor surgery such as uterine surgery, skin excision, or varicose vein strip), dentistry (dental extraction, invasive dental surgery, or dental cleaning), ENT surgery (tonsillectomy, adenoidectomy, nasal package/cauterisation under regional anaesthesia, rhinoplasty), and obstetric delivery by Caesarian section.

Treatment Protocols

Treatment with desmopressin. Desmopressin was administered in a dose of 0.3 μg/kg intravenously over 30 min. The number of DDAVP doses and the interval of administration were recorded.

Treatment with clotting factor concentrates. Data collection included details of the treatment with intermediate purity FVIII/VWF concentrates, either BPL 8Y (British Plasma Laboratory, Elstree, UK) or Haemate P (Centeon, Germany). These concentrates are manufactured from human plasma by cryoprecipitation/adsorption, using as virucidal methods dry heating (80°C for 72 hr) for 8Y and pasteurisation (60°C for 10 hr) for Haemate P.

The type of product, the preoperative dose, the postoperative dose within the first 24 hr, and the dose, duration, and frequency of treatment received after the first 24 hr were recorded. One patient received treatment with a high-purity VWF concentrate by continuous infusion on a clinical trial basis, and he was excluded from this analysis.

Antifibrinolytics. The antifibrinolytic of choice was Tranexamic acid, which was usually administered in connection with muco-cutaneous surgery, including dental surgery. The route of administration was either orally in a dose 15–20 mg/kg, four times a day, for 7–10 days or more often as a 5% mouthwash for dental procedures (10 ml, four times a day).

Laboratory monitoring. FVIII:C levels were measured by one-stage clotting assay by standard techniques. VWF activity (VWF:Ac) was measured by either ristocetin cofactor activity using fresh platelet method or by

TABLE I. Details of Treatment With DDAVP

Type of surgery	No. of surgical events (%)	No. of doses DDAVP median (range)	No. of days median (range)
Major	3 (8)	5 (2–5)	5 (2–5)
Minor	10 (27)	2 (1–6)	1.5 (1–6)
Dentistry	19 (51)	1 (1–2)	1 (1–2)
ENT	3 (8)	2 (2–4)	2 (1–4)
Total	35 (100)	2 (1–6)	2 (1–6)

our in-house ELISA assay [10]. The VWF antigen (VWF:Ag) was carried out by standard ELISA methods.

Postoperative complications. The complications considered in the postoperative period were bleeding which was either higher than expected perioperative oozing or immediately postoperative, haematoma formation, or severe bleeding which required re-intervention.

Effectiveness of haemostasis. The effectiveness of postoperative haemostasis was considered excellent if there were no bleeding or other complications, moderate if there was some bleeding but no further action was needed, and poor if there was significant bleeding that required further treatment.

RESULTS

During a ten-year period, elective surgery was performed in 27 (42%) patients with VWD who had prophylactic treatment with DDAVP and in 38 (58%) patients who received treatment with CFCs.

Treatment With Desmopressin for Elective Surgery in Patients With VWD

Twenty-seven patients with VWD had 35 planned surgical procedures under DDAVP cover. The age at the time of surgery was between 14 and 57 years, 18 patients were female, and 9 were male; 25/27 (93%) patients were type 1 VWD, and two (7%) patients were type 2M VWD. The severity of VWD in type 1 patients varied between severe (VWF:Ac 6 IU/dl) to borderline/normal (VWF:Ac 50 IU/dl). The two patients who had type 2M VWD had baseline phenotypic characteristics of FVIII:C 40 IU/dl, VWF:Ac 7 IU/dl, VWF:Ag 19 IU/dl and FVIII:C 100 IU/dl, VWF:Ac 9 IU/dl, VWF:Ag 47 IU/dl, respectively, and they both underwent dental treatment.

Details of the surgical events and treatment with DDAVP are shown in Table I.

The interval between DDAVP infusions varied between 12 and 48 hr. Tranexamic acid was added in 30/35 (86%) muco-cutaneous surgical procedures, including all 19 dentistry events. FVIII:C levels were monitored routinely on a daily basis. Within an hour post-DDAVP, a 2–3-fold increase in the FVIII:C levels was seen, with normalisation of the FVIII:C post-infusion level (in only one patient with type 1 VWD who underwent dentistry the FVIII:C raised from 16 to 38 IU/dl post-DDAVP infusion).

The effectiveness of DDAVP treatment was rated as excellent for 32 surgical events (91%). In two patients with type 1 VWD the haemostasis was moderate, as one patient had oozing following a dental extraction and required a second dose of DDAVP and one patient who underwent a hysterectomy developed a small haematoma and required six daily doses of DDAVP infusions. In only one patient with mild VWD the effectiveness of treatment with DDAVP was considered poor. This patient underwent a rhinoplasty and had two doses of DDAVP 12 hr apart. Two days later, the patient had to be readmitted to hospital with extensive bruising and secondary infection at the surgical site, and a third dose of DDAVP was given.

Treatment With Intermediate-Purity FVIII/VWF Concentrates for Elective Surgery in Patients With VWD

Between 1988 and 1997 a total of 38 patients with VWD underwent 68 surgical procedures under cover with CFCs. The median number of surgical events/year was 5 (range 0–12). The median age of the patients at the time of surgery was 42 years (range 3–77); 22 (58%) were female, and 16 (42%) were male. The classification of the patients according to the VWD type showed that 26 (68%) had type 1 VWD, 3 (8%) had type 2A VWD, 3 (8%) had type 2B VWD, and 3 (8%) had type 3 VWD. The type of CFCs used to treat the surgical events was either BPL 8Y for 52 events (76%) or Haemate P for 16 events (24%). Tranexamic acid was added in 26 (38%) surgical events, including all dental procedures.

Details of the surgery are outlined in Table II. In the postoperative period, FVIII:C levels were monitored at least once a day and the levels were kept above 50 IU/dl in all cases.

The effectiveness of haemostasis was rated as excellent in 56 events (82%) and moderate in 6 events (9%) where there was some postoperative bleeding, usually oozing or small haematomas, but no further action was needed. However, for another six events (9%) the haemostasis was considered poor, as there was significant bleeding postoperatively which required further treatment as detailed in Table III. The dosage of CFCs used to treat the bleeding complications varied between 16 and 41 IU/kg (median 27 IU/kg), and the median number of days of treatment was one (range 1–4).

DISCUSSION

This is one of the largest retrospective surveys analysing over 100 surgical procedures in patients with different types of VWD who required prophylactic treatment before surgery. The surgical events varied from oral surgery to major surgery and the haemostasis was provided

TABLE II. Details of Treatment With Clotting Factor Concentrates

Type of surgery	No. of surgical events (%)	Dose prior to surgery (IU/kg)	Dose first 24 hr postop. (IU/kg)	Postop. dose (IU/kg/day)	No. of days of Rx.
Major	10 (15)	54 (41–77)	47 (24–62)	43 (25–78)	10 (4–14)
Minor	26 (38)	48 (14–70)	26 (24–37)	37 (13–58)	4 (1–16)
Dentistry	18 (27)	34 (20–67)	–	23 (16–30)	1 (1–3)
ENT	9 (13)	48 (42–61)	32 (28–37)	32 (18–49)	6 (1–11)
Delivery	5 (7)	52 (24–62)	31 (30–31)	37 (32–43)	7 (1–13)
Total	68 (100)	48 (14–77)	31 (24–62)	37 (13–78)	4 (1–16)

TABLE III. Details of the Six Patients With Bleeding Complications Who Required Additional Treatment and in Whom the Haemostasis Was Considered Poor

VWD type	Type of surgery	Type of CFC	FVIII:C baseline (IU/dl)	FVIII:C post-infusion (IU/dl)	Dose preop. (IU/kg)	Dose postop (IU/kg/day)	Bleeding complication and additional Rx.
1	Tonsillectomy	HP	40	115	44	22	Rebleeding at 1 wk, further HP
2B	TOP	HP	68	136	49	49	Rebleeding at 2 wk, further HP
1	Caesarian section	HP	56	–	24	–	Secondary PPH Day 5, Blood Tx
3	Dental extraction	8Y	5	66	54	31	Rebleeding at Day 5, further 8Y
1	Tonsillectomy	HP	40	115	44	22	Rebleeding at Day 7, further HP
1	Cerebral angiography	8Y	40	90	34	24	Day 3 changed to HP as small haematoma present, continue until day 8

by either DDAVP or CFCs. In 1995 the results of an international prospective study on the use of FVIII concentrates in surgery and severe bleeds had analysed 76 surgical events which were covered with CFCs and emphasized the large variations in the modalities of treatment in patients with VWD at the time of surgery [7].

In our study DDAVP was used in 34% of all types of surgical procedures and it was efficacious in the majority of surgical events (91%). In one patient who did not have a DDAVP test prior surgery and underwent a rhinoplasty under DDAVP cover the efficacy of treatment was poor. These data re-emphasized the importance to assess the individual response to DDAVP in every patient in whom treatment with DDAVP is contemplated. Two patients with type 2M VWD, where DDAVP is generally considered unsuitable, were successfully managed under DDAVP cover for dental procedures. However, the role of DDAVP is not clear in the context of major surgery, but in our experience DDAVP was used with optimal results to manage three major surgical events (two appendectomies and one hysterectomy).

Tranexamic acid is particularly indicated in muco-cutaneous bleeding events, and we noticed that tranexamic acid was used more often in association with DDAVP than with CFCs. An explanation for this discrepancy is that more muco-cutaneous surgical procedures were performed under DDAVP cover than under CFCs treatment.

In the majority of surgical events CFCs were used for patients with various types of VWD where DDAVP was ineffective or contraindicated. Two types of CFCs were used: BPL 8Y and Haemate P, both of which have been shown to be highly efficacious [11,12]. The majority of surgical procedures analysed in the present study were covered with BPL 8Y (77%) as the data was collected until 1997. However, from 1997 onwards our practice changed and the concentrate of choice became Haemate P, which is one of the recent advances in the availabilities of therapies for VWD.

A recent survey published from the Nordic countries has looked at their experience in using Haemate P for patients with VWD undergoing surgery and analysed 35 surgical events covered with Haemate P or AHF-Kabi (Fraction I-O) [13]. In their experience doses of 30–40 IU/kg of Haemate-P preoperatively and between 20–30 IU/kg postoperatively with 24 hr interval were found satisfactory for a good haemostatic control. In comparison, from our study it appears that we have used higher preoperative (median 48 IU/kg, range 34–54 IU/kg) and postoperative (median 37 IU/kg, range 23–43 IU/kg) doses of CFCs. This may reflect the variation in the type and quality of CFCs that we used, as two different types of concentrates with different characteristics (BPL 8Y and Haemate P) have been used at our Centre. Moreover, in our study the dosage of CFCs was guided by the FVIII:C levels, which were consistently normalised. In contrast, in the Nordic survey neither the FVIII:C levels nor the BT were routinely monitored in connection with surgery [13]. There are other groups who similarly found that at least during oral surgery the monitoring of FVIII/VWF levels was probably not necessary [14].

Factor VIII:C levels are available in “real-time” and

therefore enable the clinician to make rapid decisions regarding dosage. In our cohort, the FVIII:C was the only parameter constantly monitored throughout all the surgical events covered with either DDAVP or CFCs and it proved sufficient to ensure an adequate haemostasis. Although monitoring of the BT has been recommended in muco-cutaneous surgery [8], in our practice we did not measure the BT in connection with surgery.

In the Nordic survey a 24-hr interval between doses was found satisfactory, whereas the manufacturer suggest that in the first three days postoperatively a 12-hr dosing interval would be appropriate. We found that the intervals between doses were ranging between 12 and 24 hr in the immediate postoperative period. The interval between doses had been individualised depending on the FVIII:C levels and the clinical response, which were closely monitored.

In our experience, the perioperative treatment with CFCs as guided by the FVIII:C levels proved safe practice, as in the majority of surgical events the effectiveness of treatment was excellent with a low complication rate. In only five surgical events (7%) the haemostasis was unsatisfactory, and these patients required additional CFCs to treat postoperative bleeding complications, which occurred despite the normalised FVIII:C levels maintained throughout the perioperative period. This is comparable with the Nordic survey where they found bleeding problems in 6% of their cohort [13]. Weather the monitoring of other parameters, such as the ristocetin cofactor activity levels, the collagen binding assay or the BT measurements would have been useful in these patients with bleeding complications is debatable. In addition, administration of platelets concentrates could also have a beneficial role by establishing and maintaining the primary haemostasis due to their content of VWF.

In the surgical context in patients with VWD pure VWF concentrates characterised by a high specific activity of VWF and a low FVIII concentration have also been used. However, a higher dose of these concentrates is required and due to the delayed elevation of FVIII, a FVIII concentrate infusion is usually given in addition. If a pure VWF concentrate is used, the monitoring of treatment relies on the FVIII:C levels and /or ristocetin cofactor activity levels [15].

In summary, during the ten-year period, the protocols of treatment used at our centre were essentially the recommendations of the UKHCDO published in 1997 [16], but we also used individualised treatment regimens. A large proportion of all types of surgical procedures were managed under DDAVP cover, which is a safer and cheaper option than CFCs. We demonstrated that with appropriate haemostatic cover the surgical risk of bleeding is similar to normal in patients with VWD. Thus, our accumulated experience provides further clinical evidence towards establishing optimal guidelines for managing surgery in patients with VWD.

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