Oral Diseases (2005) 11, 243–248

http://www.blackwellmunksgaard.com

ORIGINAL ARTICLE

Haemostatic management of intraoral bleeding in patients with von Willebrand disease

Y Morimoto[1,2], A Yoshioka[3], M Sugimoto[3], Y Imai[2], T Kirita[2]

[1]*Department of Dental Anesthesiology, Graduate School of Dentistry, Osaka University, Suita, Osaka;* [2]*Department of Oral and Maxillofacial Surgery, Nara Medical University, Kashihara;* [3]*Department of Paediatrics, Nara Medical University, Japan*

OBJECTIVES: To develop plans for the haemostatic management of intraoral bleeding in patients with von Willebrand disease (VWD).

SUBJECTS AND METHODS: Thirty-seven episodes of haemostatic management of intraoral bleeding in 19 VWD patients were analysed retrospectively based on the medical records.

RESULTS AND CONCLUSIONS: When performing tooth extractions in patients with type 1 or 2A VWD [responsive to 1-deamino-8-D-arginine-vasopressin (DDAVP)], 0.35–0.4 μg kg^{-1} of DDAVP should be administered intravenously at three times.In patients with type 2A VWD (unresponsive to DDAVP) or patients with type 2B or 2N VWD, 50–90 U [as ristocetin cofactor (VWF:RCof)] kg^{-1} of a factor VIII concentrate containing von Willebrand factor (FVIII/VWF concentrate) should be administered twice in routine extractions, and four to six times in surgical extractions.Gingival bleeding related to primary teeth can be mostly managed by pressure haemostasis alone. However, when treating gingival bleeding caused by marginal periodontitis, it is often necessary to administer 0.4 μg kg^{-1} of DDAVP or 40–70 U (as VWF:RCof) kg^{-1} of a FVIII/VWF concentrate. As local haemostasis is difficult to achieve in bleeding from the tongue or labial or mandibular haematoma, it is necessary to administer 0.4 μg kg^{-1} of DDAVP or 60–80 U (as VWF:RCof) kg^{-1} of a FVIII/VWF concentrate.In addition, oral administration of 20 mg kg^{-1} day^{-1} of tranexamic acid should be combined with the regimens described above.

Oral Diseases (2005) **11**, 243–248

Keywords: von Willebrand disease; intraoral bleeding; local haemostasis; 1-deamino-8-D-arginine-vasopressin; factor VIII concentrate

Correspondence: Yoshinari Morimoto, 1–8, Yamadaoka, Suita, Osaka 565-0871, Japan. Tel: +81 6 6879 2972, Fax: +81 6 6879 2975, E-mail: ysn-mori@dent.osaka-u.ac.jp
Received 8 March 2004; revised 13 August 2004; accepted 1 November 2004

Introduction

von Willebrand disease (VWD) is an autosomal disorder characterized by prolonged bleeding. In VWD, quantitative or qualitative abnormalities of von Willebrand factor (VWF), impaired platelet adhesion to vascular walls and platelet aggregation, thus result in a bleeding tendency (Sadler, 1994a). The mechanisms of action of FVIII/VWF are by complexing with FIII. Currently, haemostatic management protocols are being established for each type of VWD as classified by the VWF Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) (Sadler, 1994b; Eikenboom, 2001; Mazurier *et al*, 2001; Meyer *et al*, 2001; Rodeghiero and Castaman, 2001; Batlle *et al*, 2002; Laffan *et al*, 2004) (Table 1).

1-Deamino-8-D-arginine-vasopressin (DDAVP) administration increases the plasma levels of FVIII:C, VWF antigen (VWF:Ag) and ristocetin cofactor (VWF:RCof) for over an hour (Haemophilia of Georgia, 2000; Kasper, 2000; Mannucci, 2000, 2001; Pasi *et al*, 2004). The half-life of plasma FVIII/VWF is around 8–12 h (Haemophilia of Georgia, 2000; Kasper, 2000; Mannucci, 2000, 2001; Batlle *et al*, 2002; Pasi *et al*, 2004). Patients with type 1 VWD and some patients with type 2A VWD can be managed with DDAVP alone.

However, DDAVP is ineffective or contraindicated in some patients with type 2A VWD and patients with types 2B, 2N, 2M and 3 VWD. In these patients, 10–50 U (as FVIII:C) kg^{-1} of a FVIII/VWF complex concentrate is administered (Federici *et al*, 2000; Haemophilia of Georgia, 2000; Kasper, 2000; Mannucci, 2000, 2001; Piot *et al*, 2002) (Table 1).

However, few studies on the haemostatic management of surgical treatment in VWD have been undertaken and no consensus exists regarding therapeutic doses of replacement factors (Federici *et al*, 2000; Kasper, 2000; Cohen *et al*, 2001; Mannucci, 2001; Piot *et al*, 2002).

The amount of VWF in actual FVIII/VWF concentrates varies, with 1.6–2.9 units of VWF:RCof for every unit of FVIII:C, depending on the type of concentrate (Takahashi *et al*, 1987; Yoshioka *et al*, 1987; Fukui *et al*, 1988).

Table 1 Clinical and laboratory features in von Willebrand disease variants

Feature	*type 1*	*type 2A*	*type 2B*	*type 2N*	*type 2M*	*type 3*
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive[a]	Autosomal dominant	Autosomal recessive
FVIII:C	Decreased	Normal/decreased	Normal/decreased	Decreased	Normal/decreased	Absent
Plasma VWF antigen	Decreased	Normal/decreased	Normal/decreased	Normal	Normal/decreased	Absent
VWF:ristocetin cofactor	Decreased	Decreased	Normal/decreased	Normal	Decreased	Absent
Plasma VWF multimers	Normal	Absent HMW multimers	Reduced/absent HMW multimers	Normal	Normal/presence of ultra HMW multimer	Absent
Platelet VWF multimers	Normal/decreased	Normal/absent HMW multimers	Normal	Normal	Normal	Decreased/absent
VWF function	Normal	Decreased affinity for GPIb	Increased affinity for GPIb	Decreased affinity for FVIII	Decreased affinity for GPIb	Absent
Ristocetin-induced platelet aggregation	Normal/decreased	Decreased	Enhanced sensitivity at low ristocetin concentrations	Normal	Decreased	Absent
Response to DDAVP	Increase in VWF and FVIII	Variable but increase in FVIII	Contraindicated for risk of thrombocytopenia	Variable but increase in FVIII (the half-life of FVIII is significantly reduced)	Variable	None
Population (%)	70	20				10

HMW, high-molecular weight; GPIb, glycoprotein Ib; FVIII, factor VIII; VWF, von Willebrand factor; DDAVP, 1-deamino-8-D-arginine-vasopressin.
[a]Compound heterozygosity.
Information in this table is from following references: Eikenboom (2001), Mazurier *et al* (2001), Meyer *et al* (2001), Rodeghiero *et al* (2001), Laffan *et al* (2004) and Pasi *et al* (2004).

We retrospectively analysed the haemostatic management of intraoral bleeding in VWD patients treated in our department and investigated drug dosage, frequency of administration, increases in plasma VWF:RCof and local haemostasis in relation to each disease type and treatment. Based on these results, we present specific protocols for the haemostatic management of intraoral bleeding in patients with VWD.

Subjects and methods

Subjects were 19 patients who were diagnosed with VWD at the Nara Medical University Hospital and underwent 37 episodes of haemostatic management for intraoral bleeding at the Department of Oral and Maxillofacial Surgery. The medical records of these patients were examined to ascertain gender, age at treatment, dental intervention or cause of intraoral bleeding, systemic haemostatic treatments (dosage, route, and frequency of DDAVP and FVIII/VWF concentrate administration), local haemostatic treatments and postoperative bleeding.

Two FVIII/VWF concentrates were used: Haemate P^{TM} (FVIII:C:VWF:RCof, 1:2.9) (Yoshioka *et al*, 1987; Fukui *et al*, 1988) and Confact F^{TM} (FVIII:C:VWF:RCof, 1:1.6) (Takahashi *et al*, 1987). The dosage of VWF:RCof per kilogram body weight (U kg^{-1}) was calculated based on the amount of VWF:RCof included in each preparation. In addition, the level of plasma VWF:RCof has been shown to increase by 1.4% when 1 U kg^{-1} of VWF:RCof is administered (Fukui *et al*, 1988), allowing the calculation of anticipated levels of VWF:RCof following administration of FVIII/VWF concentrate.

Results

Records of 19 patients (11 men and eight women; age range: 6–49 years) with a total of 37 treatment episodes were studied. Subtypes of VWD were diagnosed with the following frequencies: type 1 ($n = 7$), type 2A ($n = 9$), type 2B ($n = 2$) and type 2N ($n = 1$). None of the patients had type 2M or type 3 VWD. In type 1 or 2A VWD responsive to DDAVP, the drug was administered intravenously. For all treatments, 20 mg kg^{-1} day^{-1} of tranexamic acid was administered orally, for electives starting from 3 h prior to surgery and at admission when treating intraoral bleeding. Treatment was continued for 1–2 weeks.

For surgical extractions, pressure haemostasis was also performed using oxidized cellulose and the surgical wound was sutured but for routine extractions or gingival bleeding, a surgical acrylic splint was used for 7 days later. Different management regiments undertaken by us for type 1, 2A, 2B and 2N VWD is given in Tables 2–4.

Discussion

Based on the results of the present study, haemostatic management of intraoral bleeding in patients with VWD is summarized in Table 5.

Table 2 Haemostatic management of patients with type 1 von Willebrand disease

Treatment or haemostasis for	*Occasion*	*Tooth number (causes of haemorrhage)*		*Agent*	*Dose (kg)$^{-1}$ and frequency*			*Local haemostasis*
		Primary tooth	*Permanent tooth (Causes of hemorrhage)*		*Day 0*	*Day 1*	*Day of splint removal*	
XLA	5[a]		6	DDAVP	0.37–0.4 μg	0.37–0.4 μg	0.37–0.4 μg	Splint
SR	3		5	DDAVP	0.35–0.4 μg	0.35–0.4 μg	0.35–0.4 μg	Suture, splint
	1		1	DDAVP	0.4 μg			Suture, splint
	1[b]		2	FVIII/VWF	90 U (126%)	70 U (98%)	70 U (98%)	Suture, splint
Scaling	1[c]			DDAVP	0.4 μg	0.4 μg		
GB	1[b]		1 (Pericoronitis)	FVIII/VWF	45 U (63%)			Splint
GB	1 (Postscaling)			FVIII/VWF	53 U (74%)			Compression
GB	2	5 (Mobility)						Compression
Haematoma of lower lip	1			DDAVP	0.4 μg			

DDAVP, 1-deamino-8-d-arginine vasopressin; FVIII/VWF, factor VIII/von Willebrand factor concentration; U, ristocetin cofactor (VWF:RCof) units; %, anticipated incremental percentage of VWF:RCof; XLA, extracted under local anaesthesia; SR, surgical extraction; GB, gingival bleeding.
[a]Two cases were performed at the same time of surgical extraction.
[b]Same patient.
[c]Scaling was performed at the same time of surgical extraction.

Table 3 Haemostatic management of patients with type 2A von Willebrand disease

Treatment or haemostasis for	*Occasion*	*Tooth number*		*Agent*	*Dose (kg)$^{-1}$ and frequency*				*Local haemostasis*
		Primary tooth	*Permanent tooth*		*Day 0*	*Day 1*	*Day 2*	*Day of splint removal*	
XLA	4	5	1	DDAVP	0.35–0.4 μg	0.35–0.4 μg		0.35–0.4 μg	Splint
	3	2	1	FVIII/VWF	54–88 U (76–123%)			54–88 U	Splint
	1	1[b]		FVIII/VWF	72 U (100%)	36 U (51%)	36 U	36 U	Splint
SR	2		4	FVIII/VWF	87–88 U (122–123%) × 2	87–88 U	87–88 U	87–88 U	Suture, splint
Scaling	1[a]			FVIII/VWF	88 U (123%) × 2				Splint
GB	4	1 (Mobility)[b]	3 (P 2; eruption 1[b])	FVIII/VWF	50–84 U (70–118%)				
GB	2	1 (Mobility)	2 (P)						Compression
Haematoma of mandible	1			FVIII/VWF	84 U (118%)				

DDAVP, 1-deamino-8-d-arginine vasopressin; FVIII/VWF, factor VIII/von Willebrand factor concentrate; U, ristocetin cofactor (VWF:RCof) units; %, anticipated incremental percentage of VWF:RCof; XLA, extracted under local anaesthesia; SR, surgical extraction; GB, gingival bleeding; P, marginal periodontitis.
[a]Scaling was performed at the same time of surgical extraction.
[b]Same patient.

Table 4 Haemostatic management of patients with type 2B and 2N von Willebrand disease

Treatment or haemostasis for	*Occasion*	*Tooth number*		*Agent*	*Dose (kg)$^{-1}$* and frequency				*Local haemostasis*
		Primary tooth	*Permanent tooth*		*Day 0*	*Day 1*	*Day 2*	*Day of splint removal*	
type 2B									
SR and fenestration of cyst	1		1	FVIII/VWF	56 U (78%) × 2	56 U × 2	56 U	56 U	Suture, splint
GB	3		5 (P)	FVIII/VWF	58 U (84%)				Compression
Tongue bleeding with laceration	1			FVIII/VWF	58 U (84%)				
type 2N									
XLA	1		1	FVIII/VWF	64 U (90%)			64 U	Splint
GB (Postscaling)	1								Compression

FVIII/VWF, factor VIII/von Willebrand factor concentrate; U, ristocetin cofactor (VWF:RCof) units; %, anticipated incremental percentage of VWF:RCof; XLA, extracted under local anaesthesia; SR, surgical extraction; GB, gingival bleeding.

Haemostatic management of tooth extraction

In most routine extractions, haemostasis was achieved by three administrations of 0.35–0.4 μg kg^{-1} of DDAVP to patients with type 1 VWD or type 2A VWD responsive to DDAVP and by two administrations of 54–88 U kg^{-1} (as VWF:RCof) of FVIII/VWF concentrate (mean, 77 U kg^{-1}) to patients with type 2A (unresponsive to DDAVP), 2B or 2N VWD. In unresponsive cases, slightly more frequent administration of a FVIII/VWF concentrate was needed.

Factor VIII/VWF concentrate was administered more often in surgical extraction when compared with routine extraction. As impacted tooth extraction or minor surgery requires a gingival incision and removal of bone, and the half-life of the concentrate is 8–12 h, it is necessary to administer drugs more frequently and for longer (for about 3 days after surgery for an average of five administrations). With these doses, the plasma concentration of VWF:RCof was anticipated to be 76–123% of normal levels during extraction, thus making it possible to achieve favourable haemostasis.

Mannucci *et al* (2002) recently investigated the amount of VWF:RCof received in patients when a FVIII/VWF concentrate was administered for the treatment of bleeding in VWD. Some of the patients in their study underwent dental treatments such as tooth extraction or scaling. They administered 20–76 U (as VWF:RCof) kg^{-1} of a FVIII/VWF concentrate (average: 60 U kg^{-1}) one to 18 times (average: three times) when performing surgical treatments in patients with type 1 or 2A VWD, and this study reported no postoperative bleeding. In addition, Federici *et al* (2000), Kasper (2000), Cohen *et al* (2001), Mannucci (2001) and Piot *et al* (2002) reported that 20–50 U (as FVIII:C) kg^{-1} of FVIII/VWF concentrate was needed for tooth extraction. These doses are equivalent to 32–145 U kg^{-1} of VWF:RCof. Furthermore, Pasi *et al* (2004) proposed the following guidelines: in tooth extraction, the activity of plasma VWF:RCof should be set at 50%, and in minor surgery, the activity of plasma VWF:RCof should be set at 100% during surgery and 50% for several days after surgery. As there are no marked differences in the dosage and frequency of drug administration between the present study and that of these reports, the above-mentioned doses appeared to be appropriate. Furthermore, the results of the present study suggest that surgical extraction requires more frequent administration of drugs when compared with routine extraction.

In gingival bleeding, haemostasis was achieved by one administration of DDAVP to patients with type 1 VWD and one administration of 45–72 U (as VWF:RCof) kg^{-1} of FVIII/VWF concentrate (average: 55.6 U kg^{-1}) to patients with type 2A, 2B or 2N VWD. As a general rule, DDAVP is sufficient in type 1 VWD. Because postoperative bleeding requires rapid and reliable haemostasis, FVIII/VWF concentrate should be used even in type 2 VWD responsive to DDAVP.

Pasi *et al* (2004) reported that, in mild intraoral bleeding, haemostasis could be mostly achieved by mouth washing or oral administration of tranexamic

Table 5 Summary of haemostatic management of patients with von Willebrand disease

		Dose (kg)$^{-1}$ and frequency				
Treatment or haemostasis for	*Agent*	*Day 0*	*Day 1*	*Day 2*	*Day of splint removal*	*Local haemostasis*
Routine extraction[a]						
Type 1 and 2A (responsive to DDAVP)						
	DDAVP	0.35–0.4 μg	0.35–0.4 μg		0.35–0.4 μg	Splint
Type 2A (unresponsive to DDAVP), 2B and 2N						
	FVIII/VWF	54–88 U (76–123%)			54–88 U	Suture, Splint
Surgical extraction or minor surgery						
Type 1 and type 2A (responsive to DDAVP)						
	DDAVP	0.35–0.4 μg	0.35–0.4 μg		0.35–0.4 μg	Splint
Type 2A (unresponsive to DDAVP), 2B and 2N						
	FVIII/VWF	56–88 U (×2) (78–123%)	56–88 U (×2)	56–88 U	56–88 U	Suture, splint
Gingival bleeding[b]						
Type 1						
	DDAVP	0.4 μg				Compression
Type 2A, 2B and 2N						
	FVIII/VWF	45–72 U (63–100%)				Compression
Haematoma						
Type 1						
	DDAVP	0.4 μg				
Type 2A, 2B, and 2N						
	FVIII/VWF	58–84 U (84–118%)				

[a]Postoperative bleeding associated with local inflammation – more frequent administration of FVIII/VWF is considered.
[b]Gingival bleeding associated with mobility of a primary tooth – local haemostasis using compression alone is adequate.
DDAVP, 1-deamino-8-d-arginine vasopressin; FVIII/VWF, factor VIII/von Willebrand factor concentrate; U, Ristocetin cofactor (VWF:RCof) units; %, anticipated incremental percentage of VWF:RCof.

acid alone. Compared with bleeding because of surgery, gingival bleeding caused by mobility of a primary tooth is easier to treat. Consequently, as pressure haemostasis can easily be performed, gingival bleeding related to primary teeth should first be treated by compression using oxidized cellulose, gauze and splinting.

When compared with gingival bleeding, local haemostasis is more difficult to achieve in haematoma of the lip or the mandible and in bleeding of tongue; as a result, a higher dose of FVIII/VWF [58–84 U (as VWF:RCof) kg^{-1}] (average: 71 U kg^{-1}) is necessary.

Mannucci *et al* (2002) reported that in patients with type 1 or type 2A VWD, an average of 45 U (as VWF:RCof) kg^{-1} (range: 14–56 U kg^{-1}) of a FVIII/VWF concentrate should be administered once on average (range: one to seven times) to treat mild bleeding. Furthermore, Kasper (2000) and Mannucci (2001) reported that 20 U (as FVIII:C) kg^{-1} of FVIII/VWF concentrate should be used for minor bleeding. This is equivalent to 32–58 U kg^{-1} of VWF:RCof. The results of the present study show that a similar dosage and frequency of the regimen for haemostasis of gingival bleeding. Soft tissue bleeding requires administration of higher doses of drugs than gingival bleeding because local haemostasis is more difficult to achieve.

In addition to these measures, tranexamic acid is recommended in all cases because it increases antifibrinolytic activity and suppresses hyperfibrinolysis in the oral tissues to facilitate intraoral haemostasis (Pasi *et al*, 2004).

References

Batlle J, Noya MS, Giangrande P *et al* (2002). Advances in the therapy of von Willebrand disease. *Haemophilia* **8:** 301–307.

Cohen AJ, Kessler CM, Ewenstein M (2001). Management of von Willebrand disease: a survey on current clinical practice from the haemophilia centres of North America. *Haemophilia* **7:** 235–241.

Eikenboom JCJ (2001). Congenital von Willebrand disease type 3 clinical manifestations, pathophysiology and molecular biology. *Best Pract Res Clin Haematol* **14:** 365–379.

Federici AB, Sacco R, Stabile F *et al* (2000). Optimising local therapy during oral surgery in patients with von Willebrand disease. Effective results from a retrospective analysis of 63 cases. *Haemophilia* **6:** 71–77.

Fukui H, Nishino M, Terada S *et al* (1988). Haemostatic effect of a heat-treated factor VIII concentrate (Haemate-P) in von Willebrand's disease. *Blut* **56:** 171–178.

Haemophilia of Georgia (2000). Protocols for the treatment of haemophilia and von Willebrand disease. *Haemophilia* **6**(Suppl.)**:** 84–93.

Kasper CK (2000). Hereditary plasma clotting factor disorders and their management. *Haemophilia* **6**(Suppl.)**:** 13–17.

Laffan M, Brown SA, Collins PW *et al* (2004). The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctor's Organization. *Haemophilia* **10:** 199–217.

Mannucci PM (2000). Desmopressin (DDAVP) in the treatment of bleeding disorders: the first twenty years. *Haemophilia* **6**(Suppl.)**:** 60–67.

Mannucci PM (2001). Management of inherited von Willebrand disease. *Best Pract Res Clin Haematol* **14:** 455–462.

Mannucci PM, Chediak J, Hanna W *et al* (2002). Treatment of von Willebrand disease with a high-purity factor/von Willebrand factor concentrate. A prospective, multicenter study. *Blood* **99:** 450–456.

Mazurier C, Goudemand J, Hilbert L *et al* (2001). Type 2N von Willebrand disease: clinical manifestations, pathophysiology, laboratory diagnosis and molecular biology. *Best Pract Res Clin Haematol* **14:** 337–347.

Meyer D, Fressinaud E, Hilbert L *et al* (2001). Type 2 von Willebrand disease causing defective von Willebrand factor-dependent platelet function. *Best Pract Res Clin Haematol* **14:** 349–364.

Pasi KJ, Collins PW, Keeling DM *et al* (2004). Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctor's Organization. *Haemophilia* **10:** 218–231.

Piot B, Sigaud-Fiks M, Huet P *et al* (2002). Management of dental extractions in patients with bleeding disorders. *Oral Surg Oral Med Oral Pathol* **93:** 247–250.

Rodeghiero F, Castaman G (2001). Congenital von Willebrand disease type 1: definition, phenotypes, clinical and laboratory assessment. *Best Pract Res Clin Haematol* **14:** 321–335.

Sadler JE (1994a). von Willebrand disease. In: Bloom AL, Forbes CD, Thomas DP, Tuddenham EGD, eds. *Haemostasis and thrombosis*, 3rd edn. Chapman and Hall Medical: London, UK, pp. 843–857.

Sadler JE (1994b). A revised classification of von Willebrand disease. *Thromb Haemost* **75:** 520–525.

Takahashi H, Tatewaki W, Nagayama R *et al* (1987). Therapeutic effect of heat-treated factor VIII concentrates in von Willebrand's disease and related disorders – studies in platelet-type von Willebrand disease. *Rinsho Ketsueki* **28:** 2117–2124.

Yoshioka A, Shima M, Nishino M *et al* (1987). In vitro characterization of various factor VIII concentrates. *Arzneim-Forsch/Drug Res* **37:** 753–756.