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Current treatment indications for von Willebrand factor concentrate

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Transfusion with blood products containing factor VIII/VWF complex is the treatment of choice for those patients (approx. 20%) who are unresponsive to DDAVP. In developed countries, virucidally treated concentrates of FVIII/VWF complex are today the mainstay of replacement therapy in von Willebrand's disease (VWD). The treatment indication for von Willebrand factor (VWF) concentrate in an individual patient has to be judged in the light of the severity of the disease and the type of hemostatic challenge. DDAVP can be used in many cases in connection with e.g. minor surgery, whereas concentrate should be used in major surgery. Recent data shows that the rate of biologic response to DDAVP is relatively low, not only in type 2 but also in type 1 VWD (about 1/3), when uniform and stringent criteria for patient selection and responsiveness are applied.[1] Type 3 VWD is unresponsive to DDAVP as these patients lack the capacity to produce or release VWF. All VWF concentrates containing FVIII tend to correct the FVIII deficiency, although they are not always effective in correcting the bleeding time. This means that it is probably better to treat mucous membrane bleedings with concentrates containing almost the full complement of VWF multimers.[2,3] Despite their inconsistent effect on the bleeding time, concentrates are used successfully, especially for control of soft tissue and per/post-operative bleeding, where the plasma coagulation system seems to be more important than the effectiveness of the primary hemostasis.

Indications by type of VWD

In type 3 VWD, concentrate is the only option as the level of FVIII is very low and the VWF is essentially lacking. In selected cases, platelet transfusions may be useful as both platelet and plasma VWF appear to be important for normal hemostasis. In patients who continue to bleed from mucosal surfaces, despite optimal replacement of plasma VWF, the addition of platelet transfusions can be effective.[4] Concentrates should also be used in type 1 and type 2 VWD if unresponsive to DDAVP. In type N VWD, the FVIII response to DDAVP is quite brief and concentrates should be considered in demanding clinical situations.

Indication by event

Severe and life-threatening hemorrhages should, in most cases, be treated using VWF-containing concentrates. If the DDAVP response is optimal and known in the specific case, DDAVP can be used. In all events where bleedings have to be controlled, and if the DDAVP response is not satisfactory, concentrate has to be used. Table 1 is extracted from Sadler *et al.*[5] and indicates doses and the number of infusions that can be used for control of bleeding episodes in patients unresponsive to DDAVP. There is also an indication for VWF-containing concentrates in prophylactic treatment of VWD, including long-term prophylaxis. In severe forms of VWD, prophylaxis may be used in a similar way as in hemophilia. Long-term prophylaxis has been used in Sweden for many years, but is not recognised or endorsed internationally. During long-term prophylaxis the FVIII component of the concentrate is probably redundant as normalization of the VWF level, or at least an increase of this level, will cause the secondary FVIII increase. However, in Swedish experience, no adverse events have been noted when using concentrates containing FVIII/VWF complex with high content of FVIII. Long-term prophylaxis can be used in type 3 VWD to prevent joint destruction, but also in both type 2 and type 3 VWD where the patients suffer from frequent and serious mucous membrane bleeds, especially from the gastrointestinal tract. In pregnancy and during delivery, there is an indication for factor concentrate in certain cases. It has to be noted that the VWF and FVIII levels tend to rise in type 1 and type 2 VWD from week 10-11 of gestation, whereas no change occurs in type 3 VWD. The levels fall rapidly after delivery and therefore bleedings may occur

Table 1. Control of bleeding episodes in patients unresponsive to DDAVP (Sadler *et al*. Thromb Haemost 2000).

Type of bleeding	*Dose (IU VIII:C/kg)*	*Number of infusions*	*Objective*
Major surgery	50	Once a day or every other day	FVIII >50 IU/dL until healing is complete
Minor surgery	30	Once a day or every other day	FVIII >30 IU/dL
Dental extraction	20	Single	FVIII >40 IU/dL
Spontaneous or post-traumatic bleeding	20	Single	

after several days in the post-partum period. The risk of bleeding at delivery is considered to be minimal if the FVIII level is >0.50 kIU/L, but significant if <0.20 kIU/L.[5] Patients who have low levels of FVIII and are unresponsive to DDAVP should be given concentrates at delivery and for at least 3-4 days into the post-partum period. For patients responsive to DDAVP, this drug should be preferred and there is also experience today of DDAVP being used during pregnancy.[6] Patients with VWD rarely develop VWF alloantibodies, but when doing so they pose a major clinical problem. Infusion with VWF-containing concentrates is ineffective and may also cause anaphylactoid reaction which can be life-threatening.[7] In cases of severe bleeding and during surgery, continuous infusion of recombinant FVIII totally devoid of VWF has been successfully used without side-effects.[8] As the VWF is lacking, the half-life of FVIII is very short and therefore high-dose continuous infusion of FVIII has to be implemented to achieve hemostatic FVIII levels.

Conclusions

Today, transfusions with blood products containing FVIII/VWF complex should only be performed using virucidally treated factor concentrates, preferably in those patients who are unresponsive to DDAVP. The treatment indication for concentrate has to be judged in the light of the severity of the disease and the type of hemostatic challenge, and in severe bleeding events concentrates should be used if the DDAVP responsiveness is unknown. Thus, the main indication is in type 2 and type 3 VWD in connection with hemorrhage or surgery or delivery. However, successful reports of long-term prophylactic treatment have been published and this mode of treatment should be further explored in order to prevent both joint disease and severe frequent mucous membrane bleeds.

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