

ZUBNÍ EXTRAKCE U PACIENTŮ S VON WILLEBRANDOVOU CHOROBOU

Dental surgery in patients with von Willebrand disease

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1 ODDĚLENÍ KLINICKÉ HEMATOLOGIE, FN BRNO

2 KATEDRA LABORATORNÍCH METOD, LF, MASARYKOVA UNIVERZITA, BRNO

3 ODDĚLENÍ DĚTSKÉ HEMATOLOGIE, FN BRNO

4 KLINIKA ÚSTNÍ, ČELISTNÍ A OBLIČEJOVÉ CHIRURGIE, FN BRNO A LF, MASARYKOVA UNIVERZITA, BRNO

5 INTERNÍ HEMATOLOGICKÁ A ONKOLOGICKÁ KLINIKA, LF, MASARYKOVA UNIVERZITA, BRNO



Plasma derived concentrates with content of VWF:RCo (FVIII) in Czech Republic – SPC

| concentrate | VWF:RCo / FVIII | VWF:RCo recovery after 1 IU / kg | | t1/2 (h) | FVIII IU / 1 mg | VWF:RCo IU/ 1 mg |
|------------------------|-----------------|----------------------------------|----------------------------|----------|-----------------|------------------|
| | | on the basis of dosage | on the basis of PK studies | | | |
| Haemate P [®] | 2.4 | 2% | 1.9% | 7 | 2 - 6 | 3 - 17 |
| Fanhdi [®] | 1.2 | 2% | 1.9% | 14 | 2.5 - 10 | 3 - 12 |
| Wilate [®] | 0.9 | 1.5 - 2% | 1.5% | 18 - 34 | ≥ 60 | ≥ 53 |
| Willfact [®] | ≥ 10 | 2% | 2.1% | 8 - 14 | | ≥ 50 |



VWF/FVIII plasma derived concentrates

| concentrate | VWF:RCo/FVIII:C | | | | SPC |
|----------------------------|-----------------|-----|------|-----------|------|
| | * | ♣ | ● | ◆ | |
| Haemate P [®] | 2.5 | 2.5 | 2.54 | 2.0-2.7 | 2.4 |
| Fanhdi [®] | 1.6 | 1.6 | 1.48 | ND | 1.2 |
| Alphanate [®] | 1.2 | 1.6 | ND | 2.04 | ≥0.4 |
| Immunate [®] | 0.16 | ND | 1.1 | 1.67 | 0.75 |
| Wilate [®] | | | | | 0.9 |
| FVIII-VHP-vWF [®] | ND | ND | ND | 4.3 – 8.5 | |
| Wilfactin [®] | 60 | 10 | ND | 8.75 | >10 |

* Federici A.B., Haemophilia 2006 ♣ Lee A.L., Textbook of Hemophilia, 2005

● Federici A.B., Haemophilia 2002 ◆ Berntorp E., Haemophilia 1999 SPC summary of product characteristics



Recommended level of VWF:RCo and FVIII:C

| bleeding type | desired level | | duration of substitution |
|-------------------|---------------------|-------------|--------------------------------------|
| | VWF:RCo | FVIII:C | |
| major surgery | > 50 (100%) | > 50 (100%) | until healing (7 - 10 days) |
| minor surgery | > 30-50% | > 30-50% | until healing (1 - 5 days) |
| dental extraction | > 50% | > 50% | for 6-12 h |
| | + antifibrinolytics | | 5 -7 days |
| bleeding episodes | > 30-50% | > 30-50% | until bleeding stops (2 - 4 days) |
| vaginal delivery | > 40-50% | > 40-50% | 3 - 5 days |

*Mannucci PM. *Blood Transfus* 2009;7:117-26 *Federici AB. *Haemophilia* 2002;8:607-21 *Nichols WL. *Haemophilia* 2008;14:171-232 *Nordic Guidelines on VWD 2008 *Pasi KJ. *Haemophilia* 2004; 10: 218-231



Difference between particular guidelines

Dental extractions:

- **UK:**

- to achieve 50% VWF:RCo
- tranexamic acid 5 days orally and/or mouthwash

- **Nordic:**

- single dose of VWF concentrate
- tranexamic acid 5-7 days orally and/or mouthwash

- **Italy:**

- > 30% FVIII:C, 6 h (2002)
- > 50% FVIII:C, 12 h (2009)

**Mannucci PM. Blood Transfus 2009;7:117-26*

**Federici AB. Haemophilia 2002;8:607-21*

**Nichols WL. Haemophilia 2008;14:171-232*

**Nordic Guidelines on VWD 2008*

**Pasi KJ. Haemophilia 2004; 10: 218-231*



VWD adult patients according to the domicile

Brno: Haemophilia A: n = 120
Haemophilia B: n = 15
VWD: n = 250 (+ 100?)



Subjects

Retrospective data since 2003

• **Single extraction:**

- Age:
 - Median: 37 years
 - Mean: 41 years
 - Range: 15 - 69 years
- Concentrates:
 - Haemate P[®]: 23
 - Fanhdi[®] : 6

- One patient twice: extraction + prostate biopsy

Multiple extractions:

- Age:
 - Median: 38 years
 - Mean: 39 years
 - Range: 8 - 74 years
- No of teeth:
 - Median: 3.5
 - Mean: 4.3
 - Range: 2 – 19
- Concentrates:
 - Haemate P[®]: 17
 - Fanhdi[®] : 3
 - Immunate[®] 1



Single dental extractions

| Patient | Age (years) | VWF:RCo (%) | VWF:Ag (%) | FVIII:C(%) | VWD type |
|---------|-------------|-------------|------------|------------|----------|
| 1 | 56 | 10 | 15 | 12 | 1Vicenza |
| 2 | 69 | 7 | 37 | 43 | 2A |
| 3 | 23 | 20 | 18 | 47 | 1 |
| 4 | 31 | 11 | 10 | 37 | 1 |
| 5 | 51 | 30 | 38 | 49 | 1 |
| 6 | 63 | 11 | 59 | 53 | 2A |
| 7 | 24 | 36 | 42 | 77 | 1 |
| 8 | 32 | 23 | 35 | 52 | 2A/E |
| 9 | 53 | 4 | 3 | 3 | 3 |
| 10 | 53 | 4 | 3 | 3 | 3 |
| 11 | 56 | 7 | 14 | 19 | 2M |
| 12 | 55 | 27 | 39 | 51 | 1 |
| 13 | 20 | 11 | 20 | 37 | 2M |
| 14 | 15 | 11 | 20 | 37 | 2M |
| 15 | 36 | 42 | 54 | 66 | 1 |



Single dental extractions

| Patient | Age (years) | VWF:RCo (%) | VWF:Ag (%) | FVIII:C (%) | VWD type |
|---------|-------------|-------------|------------|-------------|----------|
| 16 | 25 | 18 | 25 | 22 | 1 |
| 17 | 60 | 14 | 50 | 50 | 2A |
| 18 | 59 | 15 | 51 | 64 | 2A |
| 19 | 58 | 15 | 56 | 65 | 2A |
| 20 | 34 | 18 | 57 | 43 | 2A |
| 21 | 28 | 13 | 43 | 27 | 2A |
| 22 | 26 | 10 | 47 | 48 | 2A |
| 23 | 37 | 37 | 42 | 36 | 1 |
| 24 | 37 | 34 | 42 | 111 | 1 |
| 25 | 26 | 4 | 47 | 38 | 2 |
| 26 | 52 | 4 | 19 | 22 | 2 |
| 27 | 35 | 30 | 44 | 86 | 1 |
| 28 | 38 | 32....56 | 50...68 | 50...31 | 1 |
| 29 | 38 | 20 | 45 | 52 | 2A/E |



Multiple dental extractions

| Patient | Age (years) | VWF:RCo (%) | VWF:Ag (%) | FVIII:C (%) | VWD type | Teeth (No) |
|---------|-------------|-------------|------------|-------------|----------|------------|
| 1 | 12 | 1 | 2 | 4 | 3 | 3 |
| 2 | 8 | 1 | 2 | 4 | 3 | 4 |
| 3 | 31 | 8 | 72 | 36 | 2M | 3 |
| 4 | 51 | 42 | 60 | 68 | 2 | 4 |
| 5 | 68 | 20 | 76 | 47 | 2 | 5 |
| 6 | 10 | 15 | 33 | 49 | 2M | 5 |
| 7 | 8 | 6 | 29 | 33 | 2B | 5 |
| 8 | 28 | 35 | 43 | 64 | 1 | 2 |
| 9 | 54 | 32 | 57 | 74 | 2 | 2 |
| 10 | 35 | 9 | 18 | 25 | 2A/E | 2 |
| 11 | 26 | 33 | 41 | 49 | 1 | 2 |



Multiple dental extractions

| Patient | Age (years) | VWF:RCo (%) | VWF:Ag (%) | FVIII:C (%) | VWD type | Teeth (No) |
|---------|-------------|-------------|------------|-------------|----------|------------|
| 12 | 62 | 6 | 51 | 85 | 2A | 19 |
| 13 | 32 | 2 | 2 | 4 | 3 | 2 |
| 14 | 26 | 10 | 43 | 40 | 2A | 4 |
| 15 | 46 | 30 | 32 | 71 | 1 | 2 |
| 16 | 74 | 5 | 25 | 48 | 2A | 2 |
| 17 | 22 | 9 | 24 | 41 | 2 | 2 |
| 18 | 38 | 18 | 57 | 43 | 2A | 4 |
| 19 | 41 | 8 | 15 | 53 | 1 | 3 |
| 20 | 58 | 4 | 49 | 51 | 2A | 7 |
| 21 | 55 | 44 | 46 | 23 | 2N | 3 |



Dental extraction - strategy

- **Single tooth:**
 - One dose of pdFVIII/VWF: for 6 – 12 h VWF:RCo and FVIII:C > 50%
- **Multiple teeth:**
 - As a minor surgery (for 1 – 5 days)
 - Mostly 3 doses at time 0, 6 – 8 h, after next 12 h
- **Suture in every case**
- **Dental haemostatic plug (gelatine sponge):**
 - Gelaspon[®], Spongostan[®]
- **Adults:**
 - Exacyl[®] (tranexamic acid) p.o. 3x25 mg/kg or 4x15-20 mg/kg for 8-9 days
 - Without mouthwash
- **Children:**
 - Pamba[®] (paraaminobenzoic acid) in conventional dosage
 - Dicynone[®] (etamsylat) in conventional dosage



Haemate P[®] in dental extractions

+ tranexamic acid p.o. 3x25 mg/kg or 4x15-20 mg/kg for 8-9 days

| No of teeth | VWD type | | | VWF:RCo (%) | | Pre-surgery dose of VWF:Rco (IU/kg) | | No of treatment: doses / days | | Total dose of VWF:RCo (IU/kg) | |
|---|----------|----|---|--------------|------|-------------------------------------|------|-------------------------------|-----------|-------------------------------|-------|
| | 3 | 2 | 1 | median | mean | median | mean | median | mean | median | mean |
| Single | 2 | 14 | 7 | 14 (4-36) | 15.2 | 62 (32-96) | 58.3 | 1 / 1 (1-3 / 1-2) | 1.3 / 1.1 | 63 (32-192) | 70.4 |
| Multiple Median 4 Mean 4.6 (2-19) | 2 | 11 | 4 | 9 (1-42) | 14.6 | 64 (37-96) | 63 | 3 / 2 (1-17 / 1-9) | 4.8 / 2.8 | 137 (37-660) | 179.6 |

• without bleeding after extraction in the observation period except one case



Haemate P[®] in dental extractions – one case of bleeding

- Female, 51 years
- radices dent. 76- et 5++6, incip. periostitis mandibulae dx.
- VWD type probably 2A or 2M:
 - VWF:RCo 42% (30% - 56%)
 - VWF:Ag 60% (60% - 72%)
 - FVIII:C: 68% (44% - 76%)
 - PFA-100: epinephrine > 300 s, ADP > 300 s
- Haemate P[®]:
 - 1st dose: VWF:RCo 37 IU / kg
- **Tranexamic acid was not used due to repeated spontaneous echocontrast in popliteal vein**
- oozing next day:
 - 2nd dose: VWF:RCo 23 IU / kg



Fanhdi® in dental extractions

+ tranexamic acid p.o. 3x25 mg/kg or 4x15-20 mg/kg for 8-9 days

| No of teeth | VWD type | | | VWF:RCo (%) | | Pre-surgery VWF:RCo (IU/kg) | | No of treatment: doses / days | | Total dose VWF:RCo (IU/kg) | |
|--|----------|---|---|-----------------|------|-----------------------------|------|---------------------------------------|-------------------|----------------------------|------|
| | 3 | 2 | 1 | median | mean | median | mean | median | mean | median | mean |
| Single | 0 | 1 | 5 | 35.5 (11-56) | 32.2 | 32.8 (28-51) | 34.9 | 1.5 / 1 (1-3 / 1-2) | 1.7 / 1.17 | 35.5 (28-68.4) | 43.3 |
| Multiple (2-14) Median 3 Mean 3 | 1 | 1 | 1 | 10 (1-32) | 14.3 | 30 (24-40) | 31.3 | 3 / 2 (2-3 / 2) | 2.7 / 2 | 60 (24-87) | 57 |

• without bleeding after extraction in the observation period



Comparison with literature I:

Haemate P[®] in surgical interventions

**Franchini et al. Haematologica 2003;88:1279–1283*

Use of Haemate P[®] according to the type of intervention

| Intervention | Preoperative dose U VWF:RCo/kg | Days of treatment | Mean daily dose IU VWF:RCo/kg/day | Total dose IU VWF:RCo/kg |
|---------------------------|-----------------------------------|----------------------|--------------------------------------|-----------------------------|
| Major surgery (n=14) | 61.2 (47.5–81.1) | 9.7 (5.0–23.0) | 39.3 (25.0–52.5) | 284.1 (125-976.4) |
| Minor surgery (n=11) | 49.8 (42.9–61.5) | 4.2 (2.0–7.0) | 28.7 (21.4–34.8) | 120.8 (42.9-173.3) |
| Dental extractions (n=11) | 35.2 (23.5–46.1) | 1.6 (1.0–5.0) | 24.0 (23.5–25.0) | 38.4 (23.5-100.0) |
| Invasive procedures (n=7) | 43.6 (27.3–53.3) | 2.7 (1.0–5.0) | 32.3 (27.3–37.0) | 863(27.3-160.0) |
| Total (n=43) | 48.8 (27.3–81.1) | 5.7 (1.0–23.0) | 31.5 (21.4–52.5) | 183.2 (23.5-976.4) |

Values are represented as mean (range)

- Peri-operative efficacy was rated as excellent/good in all procedures, with one exception
- VWD type 1: 19 patients
- VWD type 2B: 7 patients

„Excellent = achievement of normal hemostasis

Good = mildly abnormal hemostasis not requiring additional therapy“



Comparison with literature II:

Clinical use of Haemate® P in inherited von Willebrand's disease: a cohort study on 100 Italian patients

Augusto B. Federici, Giancarlo Castaman, Massimo Franchini, Massimo Morfini, Ezio Zanon, Antonio Coppola, Annarita Tagliaferri, Elio Boeri, Maria Gabriella Mazzucconi, Gina Rossetti, Pier Mannuccio Mannucci

Intervention

| | Total dose IU VWF:RCo | Daily dose IU VWF:RCo/kg/day | Days of hospitalization (**) | Days of treatment | Number of infusions |
|------------------------------|----------------------------|---------------------------------|------------------------------------|----------------------|------------------------|
| Major surgery (n=17) | 57,600 (14,400-177,600) | 96 (53-146) | 8 (6-18) | 7 (2-18) | 7 (2-18) |
| Minor surgery (n=28) | 16,800 (4,800-55,200) | 71 (32-120) | 1 (1-10) | 3 (1-11) | 3 (1-10) |
| Dental procedures (n=19) | 7,200 (2,400-21,600) | 74 (27-124) | 0 (0-3) | 1 (1-5) | 1 (1-5) |
| Invasive procedures (n=9) | 7,200 (3,600-28,800) | 76 (47-111) | 0 (0-7) | 1 (1-5) | 1 (1-5) |
| Total (n=73) | 6,800 (2,400-177,600) | 80 (27-146) | 1 (0-18) | 3 (1-18) | 3 (1-18) |

VWD:type:
-3: No = 13
- 2: No = 27
- 1: No 23
Efficacy
excellent /
good
in 97%
patients

„Hemostasis clinically not different from normal (excellent), mildly abnormal hemostasis partial or delayed control of spontaneous bleeding or slight transient oozing from surgical wounds (good)“



Advers events

- Once **local and mild generalized rash** after infusion of various plasma derived VWF/FVIII concentrates
- Allergist suggested desensitization before administration of pdVWF/FVIII concentrate which is based on:
 - administration:
 - Intradermal
 - Intravenous in concentration increasing in geometric progression
 - Successfully implemented before Haemate P[®] or Fanhdi[®] administration for treatment of bleeding or before dental extraction or surgery without any adverse reaction
- Exacyl[®] in one dose 1.5 - 2.0 g (3 - 4 tbl): **diarrhoea**
 - Solution:
 - Divided in 4 doses a day- not exceeded 1.5g in each dose



Conclusions

Excellent efficacy of pdVWF/FVIII concentrates in dental extractions:

- suture has been used in every case
- without sealant, only gelatine plug
- in a single extraction repeated doses are mostly not necessary
- use of antifibrinolytics seems essential
- role for DDAVP:
 - not approved in Czech Republic
 - in cohort suitable for $\sim 1/4$ of patients (VWF:RCo $\geq 25\%$)
- role for etamsylat?



Thank you for your kind attention!

