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Major surgery in severe haemophilia A with inhibitors using a recombinant factor VIIa/activated prothrombin complex concentrate hybrid regimen

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Introduction

- Major surgery in haemophilia A and inhibitors is regarded as a high risk procedure but is increasingly performed with recombinant FVIIa (rFVIIa) or activated prothrombin concentrate (APCC).
- A review on the use of rFVIIa reported its total use in 395 procedures including cover for major, minor, dental and medical procedures up to 2008[1]. APCC was estimated to have been used in 210 procedures of which 61 were classified as major[2]
- Evidence of superiority of one agent over the other is lacking. Both the United Kingdom Haemophilia Centre Doctors Organisation guidelines[3] and a Canadian expert consensus document[4] suggest that either agent may be used to cover major surgery.
- Both rFVIIa and APCC have a reported success rate of 80 – 90%.
- The choice of the agent used is dependent on previous response in the treatment of bleeds, experience of the treating centre and cost. Although dosing recommendations have been made[4,2,5] the optimal regimen remain unclear.

Aim

- We report a hybrid regimen of rFVIIa and APCC (FEIBA®) in 6 total knee replacements (TKR), 1 emergency orchidectomy and 1 emergency open appendectomy in 4 patients with haemophilia A and inhibitors performed at our centre.

Methods

- All patients received rFVIIa 90µg/kg 2 hourly for at least 48 hours and switched to FEIBA® between days 2 and 5.
- At tourniquet release following total knee replacement (TKR) an extra dose of 90 - 180µg/kg was given.
- rFVIIa was reduced to 90µg/kg 3 hourly on days 2 and 3 and to 90mcg/kg 4 hourly on days 4 and 5.
- All received tranexamic acid 1gram QDS starting pre-operatively. This was stopped 12 hours before switching to FEIBA®.
- FEIBA® 200u/kg/day in three divided doses was given from day 2 to day 5, and 100–150u/kg/day in two divided doses thereafter.
- Treatment continued for 10-14 days and prior to physiotherapy thereafter.
- Post operative thromboprophylaxis was not given.

RESULTS

Patient	Treatment for acute bleeds
1. 56 year old man. Pre-op inhibitor titre 5.6	FEIBA®
2. 40 year old man. Pre-op inhibitor titre 4.2	rFVIIa for acute joint bleeds and FEIBA® for soft tissue bleeds.
3. 41 year old man. Pre-op inhibitor titre 5.3	rFVIIa
4. 38 year old man. Pre-op inhibitor 9.6	rFVIIa for acute joint bleeds and FEIBA® for soft tissue bleeds.

Patient	Procedure	Change to FEIBA®	Bleeding	Management of bleeding	Outcome
1a	TKR	Day 4	None		Full extension, flexion 85˚
1b	TKR	Day 4	None		Full extension, flexion 85˚
2	TKR	Day 4	Possible mild muscle bleed day 5 on 150 u/kg/day FEIBA®	90µg/kg every 2 hours for 24 hours then continued FEIBA®	Full extension, flexion 80˚
3	TKR	Day 6	Quadriceps haematoma day 8 on 100 u/kg/day FEIBA®	rFVIIa 90µg/kg 2 hourly reduced to 6 hourly by day 13	Full extension, flexion 95˚
4a	TKR	Day 2	Surgical bleed day 1	Ligation of spurting vessel day 3. Required 16 units RBCs in total	Full extension, flexion 90˚
4b	TKR	Day 2	a) Wound site bleeding day 1 on 90µg/kg rFVIIa 2 hourly b) Severe wound site bleeding on day 6 on 200 u/kg/day FEIBA®	a) No response to increased rFVIIa doses. Settled on FEIBA® 200 u/kg/day b) Sequential treatment. He had in total six 2 hourly doses of 105µg/kg rFVIIa and 2 twelve hourly doses of 62.5u/kg FEIBA®. Thereafter FEIBA® 200 u/kg/day was continued.	Full extension, flexion 85˚
4c	Emergency orchidectomy	Day 5	Hemiscrotum haematoma day 9 after stopping FEIBA®	Surgical drainage. Treatment with FEIBA®	Full recovery
4d	Emergency open appendectomy	Day 4	Intra-abdominal haematoma day 1 on rFVIIa 90µg/kg 2 hourly. Hb fall from 15 to 9.8 g/dl.	Settled on 150µg/kg 2 hourly for 8 hours and subsequently switched to FEIBA®	Full recovery

Discussion

- We report a hybrid regimen of rFVIIa and APCC in major surgery. To our knowledge the systematic use of such a regimen has not been reported.
- It combines the flexibility of dosing with rFVIIa in the initial postoperative period and less frequent dosing with APCC. The doses of the individual concentrates are in keeping with those suggested in the literature.
- Definite haematological bleeding occurred in 4 episodes and a possible minor bleed, but all had an excellent outcome. The bleeding episodes emphasise the high risk nature of surgery in inhibitor patients.
- Sequential treatment is not generally recommended but was used in episode 4b because of significant bleeding on maximum doses of FEIBA® and previous bleeding on rFVIIa alone.
- Large multicentre studies are needed to establish optimal treatment regimens for major surgery in inhibitor patients. These would also allow for monitoring to be further defined.

Conclusion

- We feel the hybrid regimen is a good alternative to using a single agent and has the added advantage of significant cost savings compared with rFVIIa monotherapy.

References

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