Surgical procedures and major bleeds as risk factors for the development of inhibitors in young children with Hemophilia A

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OBJECTIVES

A large proportion of children with hemophilia are diagnosed following a major hemostatic challenge such as a surgical procedure or a bleeding episode. Fresh frozen plasma and transfusions with packed red cells have often been administered prior to diagnosis of hemophilia. The development of high responder inhibitors is a major complication of treatment of hemophilia. Surgical procedures and major bleeding episodes generally require intensive factor replacement and are considered to be significant risk factors for the development of inhibitors. The objective of this study was to determine whether children presenting with major bleeds and/or surgery at diagnosis were at greater risk for the development of high responder inhibitors (HRI).

METHODS

A retrospective single centre study was undertaken in previously untreated patients with severe hemophilia A (FactorVIII <1%). All patients were treated for a minimum of fifty exposure days with a single product (Intermediate purity plasma derived solvent detergent treated Factor VIII/ VWFactor concentrate – Haemosolvate®, Natal Bioproducts Institute). Medical records were available in this Hemophilia Treatment Center(HTC) on all patients since the introduction of this product in 1990. All records on consecutively registered patients were analysed from 1990 to 2014. Data relating to the presenting symptoms, signs, surgical procedures, Fresh frozen plasma(FFP) or red cell transfusions, ethnicity and family history was collected. The standard of care was on demand episodic treatment (92); primary prophylaxis (6); secondary prophylaxis(5). The patients were closely monitored for the development of inhibitors (measured in Bethesda Units) during the first 50 exposure days. Wherever possible elective surgical procedures were not performed during the first 50 exposure days.

Inclusions

Total patients included 139 (prior to exclusions)

Exclusions

Total patients excluded - 36

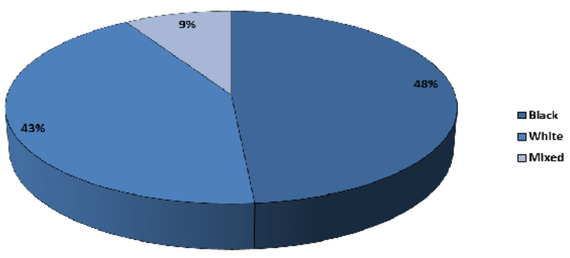
- >6 years at diagnosis (9)
- <50 exposures days (14)
- Lost to follow up (2)
- Transfers (3)
- Other factor concentrates (8)

Definitions

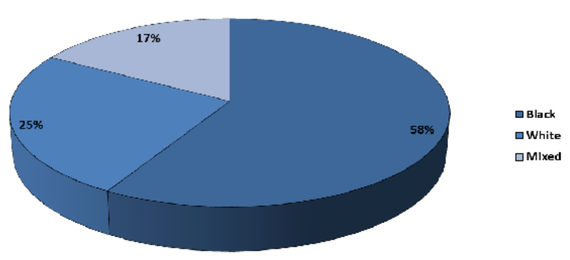
Exposure day(ED): All factor given on a calender day
Mild bleeds: less than 3 consecutive exposure days
Major bleeds including surgery: > than 3 consecutive ED
HR inhibitor (HRI): > 5 BU on two consecutive tests
Family History positive (+): if known family history of Hemophilia at diagnosis.

Graphs and tables

Ethnic Groups



High Responder Inhibitors Total 12



PRESENTING FEATURES PRIOR TO DIAGNOSIS AND RELATION TO HR INHIBITOR DEVELOPMENT

	TOTAL	BLACK	WHITE	MIXED*	HR INHIB
COHORT	139	72	54	13	12
EXCLUSIONS	36	22	10	3	0
MILD BLEED	24 (23%)	13	9	2	0
MAJOR BLEED	61 (59%)	32	23	3	11
FAMILY HISTORY +	18 (18%)	8	10	0	1
HR INHIBITOR	12 (12%)	7	3	2	12

RESULTS

- Total patients included (post exclusions): 103
- Mean age at diagnosis: 19 months (range 0.2 – 68 mths)
- Major bleeds at first exposure: 61 patients (59%)
  - Black 32 pts; White 23 pts; Mixed 3 pts
- Mild bleeds at first exposure: 24 patients(23%)
- Known family history of Hemophilia: 18 patients (18%)
- High Responder Inhibitors: 12 patients (12%)

Characteristics of the HR Inhibitor patients (12)

- Mean exposure days: 18 (range 8 – 75; 10 pts <20 ED)
- Mean age: 30 months (range 6 – 110 months)
- Ethnicity: Black 7 pts; White 3 pts; Mixed 2 pts
- Genetic mutation: 6 Intron 22 inversion; 1 other; 5 not done.
- Family History of HRInhibitor: 1 patient
- Major bleeds or surgery at first exposure: 11/12 pts

CONCLUSIONS

The results from this retrospective study suggest that major bleeding and/ or surgery requiring red cell / FFP and intensive factor concentrate replacement at first exposure to factor concentrates were the most important determinants for the development of HR inhibitors. Black African and Mixed (Black African and White parentage) ethnicity was a contributing risk factor. Genotyping was not performed on all the patients in this study.

REFERENCES:

1. P.W. Collins, J Thromb Haemost 2007; 5: 1380-2.
2. S.C. Gouw, et al. J Thromb Haemost 2007; 5: 1383-90.
3. P.S. Maclean, et al. Haemophilia 2011; 17: 282-287.
4. K. Kurnik, et al. Haemophilia 2010; 16(2): 256-262.