



# RISK OF BLEEDING AND INHIBITOR DEVELOPMENT AFTER CIRCUMCISION OF PREVIOUSLY UNTREATED(PUPs) OR MINIMALLY TREATED(MTPs) SEVERE HEMOPHILIA A PATIENTS

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## INTRODUCTION

Circumcision is a traditional ceremony in Egypt, an important social problem for the hemophiliac child and his family. Accordingly; parents are willing to take the risks of circumcision to fulfill their religious and social beliefs. Inhibitor development is the major treatment complication in children with severe hemophilia A. The incidence of inhibitors depends on both genetic and non genetic factors influence inhibitor development as : age at first treatment, intensity of treatment ,vaccination, infection, breast feeding and surgery. The maintenance of effective haemostasis in such patients is significantly more difficult and substantially more expensive .

## AIM OF THE WORK

The purpose of this study was to evaluate post-circumcision bleeding after low dose FVIII replacement in addition to time and rate of inhibitor development over a 12 month period in young severe hemophilia A.

## SUBJECTS AND METHODS

### Patients

A total of 42 patients (PUPs; n=24 or (MTPs; n=18) with severe hemophilia A less than three years old were enrolled in this one year prospective study. Eighteen (PUPs; n=10 and MTPs; n=8) were circumcised at our institution during 2009 while parents of the other twenty-four( PUPs; n=14 and MTPs; n=10) decided to postpone circumcision to beyond the study period. Both groups were followed up for 12 months from study entry for evaluation of inhibitor development every eight exposure days (EDs). All were treated exclusively with a single plasma-derived factor VIII product on demand therapy.

### Methods:

#### Pre-operative management :

All patients were admitted on the day of circumcision four hours prior to surgery. Homeostasis plan was designed as follows: One hour before circumcision, first dose of factor concentrate was given to the patients 25 U/kg and pre-operative intravenous tranexamic acid (25 mg/ kg) once was applied to all cases.

#### Operative management ( Surgical technique) :

Circumcision was carried out under general anesthesia and acetaminophen(paracetamol) suppositories instead of local penile block used in other cases of circumcision. The prepuce was incised circumferentially and excised using bone cutting forceps and cutting the prepuce using heated blade cautery. The wound was covered with a Vaseline gauze dressing to ease its removal without detachment of possible crust. The dressing was removed 5-7 days after the operation.

#### Post-operative management:

The patients were observed in the hospital after the procedure, were discharged 4-6 hours after circumcision, analgesics were given whenever needed and antibiotic ointment was applied to the wound. Parents were instructed to observe any bleeding and to come immediately to allow prompt early intervention. One week later, they were seen in outpatient hematology clinic; with report on healing and cosmetic appearance

Table (2): Demographic data of the patients who developed inhibitors

Patient No.	Age at circumcision and /or evaluation(months)	Age at first exposure to factor VIII(	Age at development of inhibitor	No. of previous exposure days before	No. of EDsAt which developed inhibitor	No. of bleeding episodes	Peak inhibitor titre (BU/ml)	Total factor VIII used (u/kg/year)	Family history Of inhibitor
1*	12	12	16	-	8	10	44	380	-
2*	8	8	20	-	16	11	20	400	+
3*	19	16	22	4	40	18	91	680	-
4	14	8	11	3	8	7	33	240	+
5	24	25	30	-	16	9	25	460	-
6	7	10	15	-	16	11	55	420	-
7	21	18	26	4	64	19	158	760	+

\*Circumcised patients

## RESULTS

- The frequency of bleeding after circumcision was 5.5% (n = 1).
- Only the patient with previous inhibitor had bled twice; on day 5 which responded to a single dose of factor VIII(50 units/Kg) and on day 7 post-circumcision, where haemostasis was achieved only after a single dose of Recombinant Factor VIIa (90 microgram/kg),followed by application of an absorbable gelatin sponge to the site of bleeding in conjunction with pressure, and binding).
- None of patients had bleeding intra-operative or in the first four days after procedure. No other complications were encountered. The period of complete wound healing varied between 7 and 14 days (median 8 days) .
- High-titer inhibitors developed in seven; three patients circumcised group (16.6 %) after a median of 16EDs (8-40) in contrast to four patients (16.6 %) developed high titer inhibitor in the non circumcised group; after a median of 16 EDs (range 8–64).
- The two patients in each group who had low- titer inhibitor (<5 BU mL), one of them cleared inhibitors spontaneously; the other one treated with immune tolerance induction.

## CONCLUSION

No bleeding following circumcision was encountered using low dose FVIII except in a low titer inhibitor infant necessitating administration of Recombinant Factor VIIa and local haemostatic measures. Moreover, circumcision was not a risk for development of inhibitor where the incidence of high- titer inhibitors during12 months follow up was low in this cohort of PUPs or MTPs patients and comparable to non circumcised.

Table(1):Characteristics of enrolled patients in the study

Parameter	Circumcised (n=18)		Non circumcised (n=24)		P value	Adjusted p value
	Median	(Range)	Median	(Range)		
Age at diagnosis (weeks)	4	(1-16)	6	(1-18)	0.021	0.147
Age at circumcision and /or evaluation (months)	19	(8-34)	24	(4-33)	0.001	0.007
Weight at evaluation(kg)	10	(8-13)	12	(6-14)	<0.001	0.007
Number of EDs	36	(16-72)	32	(12-72)	0.193	1.000
Factor VIII used during 12 months follow up(u/kg)	640	(480-980)	620	(300-900)	0.495	1.000
<b>Complication</b>						
Patients who Developed inhibitor	3	(16.7)	4	(16.7)	1.000	1.000
Total bleeding episodes/ Pt	11	6-33	12	6-32	0.468	1.000

