

**SITUATIONS HORS-AMM
POUR LESQUELLES
L'INSUFFISANCE DES DONNÉES
NE PERMET PAS D'ÉVALUER
LE RAPPORT BÉNÉFICE/RISQUE**

HEMOLEVEN®

Traitement préventif ou curatif des hémorragies chez les patients présentant un déficit modéré en facteur XI

- **Traitement préventif ou curatif des hémorragies chez les patients présentant un déficit modéré en facteur XI**

Les déficits héréditaires en facteurs de la coagulation en dehors de l'hémophilie ont un certain nombre de points communs: transmission autosomale récessive sauf pour le déficit en facteur XI (FXI), déficits quantitatifs et souvent qualitatifs. Le déficit en facteur XI est une anomalie rare (prévalence de 1/1 000 000 dans la population générale) mais fréquente dans certaines populations, comme la population juive ashkénaze (prévalence variant entre 4 et 11%) ou la population basque. Le diagnostic d'un déficit en facteur XI, est le plus souvent porté de façon fortuite car les complications sévères sont rares.

Les déficits sévères (sujets homozygotes ou hétérozygotes composites) en FXI sont considérés habituellement comme tels pour des taux < 10-15% voire 20%. En pratique, les déficits modérés sont définis pour des taux compris entre 20 et 60-70 % ; ils sont associés à un risque hémorragique difficile à appréhender car il n'y a pas de corrélation franche entre le degré de sévérité et le risque hémorragique. A 30-40 % de FXI voire plus, un sujet hétérozygote peut avoir un réel risque hémorragique post-traumatique ou en postopératoire. C'est une particularité de ce type de déficit.

L'insuffisance des données ne permet pas d'évaluer le rapport bénéfice-risque d'Hémoleven® ni dans la prévention des hémorragies ni dans le traitement des complications hémorragiques sévères chez les patients présentant un déficit modéré en FXI.

- En prévention des hémorragies, les patients ayant un déficit modéré en FXI et qui pourraient bénéficier d'Hémoleven® ne sont pas clairement identifiés en raison de la mauvaise corrélation qui existe entre ce risque et le taux de FXI.
- Dans le traitement des complications hémorragiques sévères, aucune étude ne compare Hémoleven® aux traitements de première intention, à savoir les anti-fibrinolytiques tels que l'acide tranéxamique ou les moyens d'hémostase locale. De même, la place d'Hémoleven® par rapport au Plasma Frais Congelé est mal définie. Par ailleurs, il n'existe pas de consensus pour définir les chirurgies « à risque ».

Enfin, les risques liés à l'utilisation d'Hémoleven® sont à prendre en compte : thrombose, CIVD, infarctus du myocarde, embolie pulmonaire.

Effet d'Hémoleven dans les déficits modérés en FXI

Auteur	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Goudemand (1996)	Ouverte N = 31 patients devant avoir une chirurgie (5 à 76 ans) et recevant du FXI en prophylaxie . n = 22 patients avec FXI < 10 % . n = 9 patients avec FXI entre 11 et 50 %	FXI : 1-14 perfusions / patient avec un total de 152600 unités		Dosage des marqueurs de la coagulation	- ↑ modérée des F1+2 de la thrombine et TAT avec un pic à 6h post-perfusion et retour à la normale 12 h après. - D-dimères restent élevés pendant environ 72 h - Effets indésirables : . hématurie chez 1 patient (FXI basal : 11%) malgré un taux de FXI maintenu > 27%. . CIVD quelques heures post-perfusion de 41-60 U/kg de FXI chez 3 patients (>60 ans) dont 1 patient 10 jours plus tard a développé une thrombose veineuse puis une embolie pulmonaire.
Cobo Rodriguez (2004)	Ouverte N = 15 patients déficitaires en FXI en pré-op et recevant du FXI en prophylaxie .n = 8 patients avec une	FXI : 10 UI/kg/48h			Efficacité clinique : pas de saignement Pas d'effet indésirable thrombotique

	<p>autre coagulopathie (von Willebrand type I, déficit modéré en FIX, déficit modéré en FXII et ITP)</p> <p>.n = 7 patients (5 déficits modérés et 2 légers) de 22 à 57 ans sans inhibiteurs du FXI</p>				
Collins (1995)	<p>Rétrospective N = 25 patients (45 épisodes hémorragiques) recevant du FXI en prophylaxie Comparative versus 103 patients avec ou sans traitement PFC</p>	FXI ou PFC			<p>Patients traités en prophylaxie par FXI : pas de saignement mais :</p> <ul style="list-style-type: none"> . 1 décès d'un infarctus chez un patient avec des antécédents de maladie cardiovasculaire, . 1 patient victime d'un épisode ischémique à J3 le jour de l'injection de FXI, . 1 patient victime d'une embolie pulmonaire bilatérale 7 sem après un traitement prolongé par FXI.

PFC : plasma frais congelé TAT : complexes thrombine-antithrombine CIVD : coagulation intra-vasculaire disséminée

F1+2 : peptide d'activation de la prothrombine (marqueur de l'activation du FII en FIIa)

Bibliographie

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- 2-T Cobo Rodriguez, V Gimenez Yuste, R Chaves-Machado, A Villar-Camacho, M Quintana-Molina and F Hernandez Navarro Factor XI deficiency, a single center experience in management of patients undergone to surgery under treatment with FXI concentrate. Haemophilia 2004, 10 (suppl 3) : 7
3. Clinical experience of factor XI deficiency : the role of fresh frozen plasma and factor XI concentrate. Collins PW, Goldman E, Lilley P, Pasi KJ, Lee CA. Haemophilia 1995, 1, 227-231
- 4-Smith JK Factor XI deficiency and its management Haemophilia 1996 ; 2 : 128-136
- 5-Aledort LM, Goudemand J; Hemoleven Study Group. United States'factor XI-deficiency patients need a safer treatment. Am J Hematol. 2005 Dec;80(4):301-2.
- 6-Kadir RA, Kingman CE, Chi C, O'connell NM, Riddell A, Lee CA, Economides DL. Screening for factor XI deficiency amongst pregnant women of Ashkenazi Jewish origineHaemophilia. 2006 Nov;12(6):625-8.
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14. Heredity and coagulation studies in ten families with Factor XI (plasma thromboplastin antecedent) deficiency. Leiba H, Ramot B, Many A. Br J Haematol. 1965 Nov;11(6):654-65 : no abstract

Résumé Abstracts

A four year experience of a pure factor XI concentrate

Goudemand J, Aurousseau MH, David B, Denninger MH, De raucourt E, Dieval J, Fressinaud E, Gouault M, Pernod G, Porte A, Pouzol P, Stieltjes N, and Verroust F (xxème International congress of the world Federation of hemophilia, Dublin, 1996).

Patients with factor XI(FXI) deficiency can suffer haemorrhagic diathesis requiring correction of the defect. This can be achieved by using fresh frozen plasma but this treatment has some limitations. A pure FXI concentrate (SA>100 U/mg) was available in France since 1992. The product (hemoleven) is prepared through conventional chromatography and treated with solvent detergent in association with nanofiltration. Heparin and more recently C1 esterase are added in the concentrate. Hemoleven has been used in 31 French patients aged 5 to 76 yr to cover 33 various surgical procedures. The FXI level was less than 10% in 22 cases and ranged from 11 to 50% in the others. As a whole the patients received 91 infusions (1-14/patient) and a total of 152600 units. Twelve patients received a single infusion (35U/kg) apart from bleeding or surgery which allows to measure the half-life : 45.5+/- 7.9 h (33-56) and recovery : 1.85+/-0.38%/U/kg (1.30-2.38). Coagulation activation markers were followed in a limited number of patients: a moderate increase in F1+2 and TAT was observed peaking at 6h and returning to normal within 12h. D-dimers remained elevated for approximatively 72 h. One bleeding complication occurred in a patient (basal FXI: 11%) treated for a junction syndrome who developed post-operative hematuria despite FXI concentration kept >27%. Three patients (>60 yr old) developed DIC, followed 10 days later in one patient by venous thrombosis and PE. DIC occurred a few hours later the patients received a dosage of 41-60 U/kg. Lastly it has been possible to detect in some patients an activation of coagulation without evidence of clinical thrombosis. Based on this experience it appeared that dosages should not exceed 30U/kg. Basal FXI concentrations and clinical history have also to be considered in order to check if lower dosages could not be used. However it is especially difficult in FXI deficiency to correlate FXI level and risk of bleeding. Subsequent infusions (15-30U/kg) should not be repeated more frequently than 2-3 days. There are not clear explanations of thrombogenic risk of FXI concentrates. It is not known if this risk is linked to FXI by itself or other components present in the product. This should be précised to definitely fix the therapeutic guidelines of FXI concentrates.

Factor XI deficiency and its management

Factor XI deficiency, a single center experience in management of patients undergone to surgery under treatment with FXI concentrate.

T Cobo Rodriguez, V Gimenez Yuste, R Chaves-Machado, A Villar-Camacho, M Quintana-Molina and F Hernandez Navarro Haemophilia 2004, 10 (suppl 3) : 7

Factor XI deficiency is an uncommon autosomally inherited coagulation disorder occur more frequently in a number of well-defined populations (ashkenazi descent and the basque population of southern France). It is characterized by prolongation of activated partial thromboplastin time with normal prothrombin time. It is associated with variable clinical phenotype. It rarely produces spontaneous bleeding although patients with disorder are at risk for haemorrhagic complications after trauma or surgery, or challenges to haemostasis. We describe our experience in the management of FXI deficiency in surgery procedures. We have 75 cases of deficiency of FXI, eight of them associated with another coagulopathy disorders like von Willebrand disease type I, mild deficiency of FIX, mild deficiency of FXII and ITP. We report seven cases, five moderate and two mild, without inhibitor against FXI. They were undergone to surgery under prophylaxis with hemoleven (LFB) at dose 10UI/kg/48h. There were four males (22-57 years old) (one of them with von willebrand disease) and three males (variable range of age: 1-57). The surgery procedures were: knee surgery, hysterectomy and double anexectomy by endometrial adenocarcinoma, dental extraction and delivery, in the female group and prostatectomy, septorhinoplasty and phimosis in the male group. We found: clinical efficacy of FXI concentrate, hemoleven at dose of 10UI/kg, no evidence of bleeding, post-surgery and no evidence of thrombotic episodes despite of age and clinical features like neoplasm. At conclusion, Hemoleven is effective and safety treatment at dose established in patients who undergone surgery.

Clinical experience of factor XI deficiency : the role of fresh frozen plasma and factor XI concentrate. Collins PW, Goldman E, Lilley P, Pasi KJ, Lee CA. Haemophilia 1995, 1, 227-231

Summary. Factor XI deficiency is a rare autosomally transmitted coagulopathy that is associated with a variable bleeding tendency. Recently there have been reports of thrombotic events following the administration of a virally inactivated factor XI concentrate (BPL) to factor XI deficient patients. We have therefore reviewed a single centre's experience of the use of factor XI concentrate over a 6-year period and compared this to our previous experience of either no treatment or treatment with fresh frozen plasma (FFP) in 103 patients. There were 156 procedures performed without haemo- static cover. The incidence of bleeding was greatest following tonsillectomy (71%) and dental extraction (SI'h). There was a trend for bleeding complications to be associated with lower levels of factor XI but patients with all levels of factor XI suffered bleeding complica- tions. There were

38 procedures carried out under FFP cover, with only one patient suffering excessive bleeding and no serious complications. Factor XI concentrate was given to 25 patients to cover 45 episodes. There were no bleeding complications. Three patients suffered serious complications. One patient, with a previous history of cardiovascular disease, died of a myocardial infarction and a second had an ischaemic episode resulting in a %day hospital admission. These episodes both occurred on the same day as the factor XI infusion. A third patient suffered bilateral pulmonary emboli 7 weeks after a prolonged course of factor XI concentrate. These findings suggest that factor XI concentrate should be contraindicated in patients with a history of cardiovascular disease, when FFP should be used. Guidelines for the use of factor XI concentrates should be revised, and work performed to establish the mechanism of these thrombotic events.

Factor XI deficiency and its management
Smith JK. Haemophilia 1996; 2 : 128-136

United States factor XI-deficiency patients need a safer treatment.
Aledort LM, Goudemand J; Hemoleven Study Group. Am J Hematol. 2005 Dec;80(4):301-2.

A replacement factor for Factor XI which is virally inactivated is not available in the U.S. Elsewhere an inactivated concentrate has been used. A review of the experience over 15 years suggests that this product is safe and effective and suggests its potential use in the U.S. The most serious complication of the factor was a slight increase in DIC and thrombotic events.

Screening for factor XI deficiency amongst pregnant women of Ashkenazi Jewish origin
Kadir RA, Kingman CE, Chi C, O'Connell NM, Riddell A, Lee CA, Economides DL. Haemophilia. 2006 Nov;12(6):625-8.

A pilot study was conducted over a 6-month period to evaluate antenatal screening for factor XI (FXI) deficiency amongst Ashkenazi Jewish women booking for their pregnancy in a single obstetric unit. Fifty-four women of Ashkenazi Jewish origin were recruited during their visit for the routine first trimester ultrasound scan. They completed a questionnaire about their personal bleeding symptoms and had blood taken for FXI levels (FXI:C). Seven (13%) women had partial FXI deficiency. Five (9%) were newly diagnosed, and in the remaining two, the diagnosis was known previously. One infant with severe FXI deficiency was identified as a result of maternal testing. This study has shown that FXI deficiency is common amongst women of Ashkenazi Jewish origin and supports its antenatal screening in this population. However, further studies are required to evaluate its cost-effectiveness and the effect on pregnancy outcome.

Plasma replacement therapy during labor is not mandatory for women with severe Factor XI deficiency
Salomon O, Steinberg DM, Tamarin I, Zivelin A, Seligsohn U. Blood Coagul Fibrinolysis. 2005 Jan;16(1):37-41

Severe factor XI deficiency is an injury-related bleeding disorder. The risk of excessive post-partum hemorrhage in affected women has so far been evaluated in a relatively small number of patients and it is uncertain whether prophylactic treatment with fresh frozen plasma or factor XI concentrate is needed during or after vaginal or cesarean delivery. We retrospectively analyzed bleeding manifestations related to vaginal and/or cesarean deliveries in a cohort of 62 women with factor XI activity < 17 U/dl and evaluated whether replacement therapy is essential. Fifty-one women had 139 vaginal deliveries, six women had 13 cesarean deliveries, and five women had seven vaginal as well as five cesarean deliveries. Forty-three of the 62 women (69.4%) never experienced post-partum hemorrhage during 93 deliveries (85 vaginal, eight cesarean). Hemorrhage occurred in 19 women, which in six women accompanied each one of their 17 vaginal deliveries. Post-partum hemorrhage had no relationship with the abnormal genotype that caused factor XI deficiency nor with factor XI level. These observations suggest that the use of fresh frozen plasma or factor XI concentrate during and/or after vaginal delivery is not mandatory in women with severe factor XI deficiency and can be reserved for patients who develop excessive hemorrhage. For women requiring cesarean section it appears that the same policy can be advocated but more observations are needed.

Factor XI deficiency and its management
Bolton-Maggs PH. Haemophilia. 2000 Jul;6 Suppl 1:100-9.

Factor XI deficiency has a more variable bleeding tendency than haemophilia A or B. Individuals with severe deficiency have only a mild bleeding tendency, which is typically provoked by surgery, but the risk of bleeding is not restricted to individuals with severe deficiency. The bleeding tendency varies between individuals with similar

factor XI levels, and sometimes the bleeding tendency of an individual may vary. The reasons for this are not fully understood, although in cases of severe deficiency there is some correlation between phenotype and genotype. Factor XI is activated by thrombin. The role of factor XI in physiological processes has become clearer since this fact was discovered, and the discovery has contributed to a revised model of blood coagulation. Factor XI deficiency occurs in all racial groups, but is particularly common in Ashkenazi Jews. The factor XI gene is 23 kilobases long. Two mutations are responsible for most factor XI deficiency in the Ashkenazi population, but a number of other mutations have now been reported in other racial groups. Individuals with factor XI deficiency may need specific therapy for surgery, accidents, and dental extractions. Several therapies are available which include fresh frozen plasma, factor XI concentrates, fibrin glue, antifibrinolytic drugs, and desmopressin. Each has advantages and risks to be considered. Factor XI concentrate may be indicated for procedures with a significant risk of bleeding especially in younger patients with severe deficiency, but its use in older patients has been associated with thrombotic phenomena. If fresh frozen plasma is to be used it is preferable to obtain one of the virally inactivated products. Fibrin glue is a useful treatment which deserves further study

Bleeding problems in factor XI deficient women
Bolton-Maggs PH. *Haemophilia*. 1999 May;5(3):155-9

Factor XI deficiency affects both sexes. Some bleeding problems are specific to women, and have been overlooked in the past. Women with factor XI deficiency are prone to menorrhagia and to bleeding complications after childbirth. These may occur in women with partial deficiency, as well as in those with severe deficiency. Instrumental delivery and gynaecological surgery need careful planning in such women with close collaboration between the obstetrician and haematologist.

Factor XI deficiency: genetic and clinical studies of a single kindred
Litz CE, Swaim WR, Dalmaso AP. *Am J Hematol*. 1988 May;28(1):8-12

A four-generation 25-member kindred with Factor XI:C deficiency is reported. Factor XI:C levels in heterozygotes varied from 15 to 58%, suggesting that Factor XI:C values for homozygote determination should be less than 15%. The frequency of bleeding was not correlated with Factor XI:C levels in this range. Individuals with joint pain had significantly lower Factor XI:C levels than members without joint pain and pain occurred more frequently in frequent bleeders. Lod scores showed no close genetic linkage of Factor XI:C deficiency with blood group MNSs (chromosome 4), complement components Bf and C4B (chromosome 6), or blood group P.

Definition of the bleeding tendency in factor XI-deficient kindreds-a clinical and laboratory study
Bolton-Maggs PH, Patterson DA, Wensley RT, Tuddenham EG. *Thromb Haemost*. 1995 Feb;73(2):194-202

Individuals with severe factor XI deficiency are prone to excessive bleeding after injury or surgery, but the existence of a haemorrhagic tendency in partial factor XI deficiency is controversial. In this study, 172 members of 30 kindreds (20 non-Jewish) transmitting factor XI deficiency in North West England were interviewed and a bleeding history questionnaire completed. Blood was taken for coagulation assays. The questionnaires were categorised independently by two assessors to determine presence or absence of a bleeding tendency, in the absence of information about the factor XI level or family history. Analysis shows that 48% of heterozygotes have a bleeding tendency. Eighteen (60%) families came to attention because of bleeding problems in heterozygotes. Comparison of histories between partially deficient and non-deficient individuals demonstrated a higher incidence of menstrual problems, an increase in significant bruising, and an increased likelihood of excessive bleeding after tonsillectomy and dental extractions. The incidence of von Willebrand's disease was not increased, but individuals with heterozygous factor XI deficiency who were bleeders tended to have lower levels of factor VIIIc and von Willebrand factor, and were more commonly of blood group O. These features may contribute to the bleeding tendency. There was no evidence of alteration in factor VII activity (as defined by the ratio of activity to antigen) between the bleeders and non-bleeders. This is convincing evidence for abnormal bleeding in factor XI deficiency which is not confined to severely deficient patients.

Inheritance and bleeding in factor XI deficiency
Bolton-Maggs PH, Young Wan-Yin B, McCraw AH, Slack J, Kernoff PB. *Br J Haematol*. 1988 Aug;69(4):521-8

.A study of 20 Jewish and four non-Jewish kindreds transmitting factor XI deficiency (164 individuals) confirmed inheritance to be autosomal with severe deficiency in homozygotes (mean factor XI level 3.8 u/dl, SD 2.91) and partial deficiency in heterozygotes (mean factor XI level 57 u/dl, SD 10.42; normal mean factor XI level 96 u/dl, SD 11.6). The probability of an individual being heterozygous can be predicted from the factor XI level using a graph derived from this data. The accuracy is increased by including the prior probability derived from the pedigree. A high frequency of heterozygote to heterozygote mating was observed in the Jewish families

consistent with an estimated gene frequency of 13.4% in this racial group. The relationship between factor XI level and bleeding tendency is poor; a third of heterozygotes had bled excessively after surgery, including six with factor XI levels above 50 u/dl, showing this condition to have clear signs of expression in heterozygotes. The lower limit of the normal range (2 SDs from the mean) was found to be 72 u/dl.

The mode of inheritance of PTA deficiency: evidence for the existence of major PTA deficiency and minor PTA deficiency. RAPAPORT SI, PROCTOR RR, PATCH MJ, YETTRA M. Blood. 1961 Aug;18:149-65 : no abstract

Heredity and coagulation studies in ten families with Factor XI (plasma thromboplastin antecedent) deficiency. Leiba H, Ramot B, Many A. Br J Haematol. 1965 Nov;11(6):654-65 : no abstract
