Surgery in Patients with Congenital Factor VII Deficiency (Congenital Hypoproconvertinemia)
Experience with One Case and Review of the Literature

By Herbert S. Strauss

SURGERY POSES a maximal challenge to the hemostatic mechanism of the individual and may be life-threatening in patients with certain hemostatic defects, unless protection is offered by proper replacement therapy. Whereas considerable experience has been gained in the control of surgical bleeding in such relatively common disorders as hemophilia A and B, and von Willebrand's disease, experience is scanty in certain other rare coagulation defects, such as congenital Factor VII deficiency (congenital hypoproconvertinemia). Of the latter entity only 46 authentic cases have been published to date.1-29 Of the patients who underwent surgery, without replacement therapy, some—but not all—surprisingly had no bleeding difficulties. With replacement therapy none of the patients had any excessive bleeding during or after surgery, but detailed documentation regarding infusion therapy and the Factor VII levels achieved is lacking. Knowledge of required replacement therapy in association with surgery is not only important from a practical point of view, but also throws some light on the physiologic role in hemostasis of the deficient clotting factor. In the present report, our recent experience with a previously published case1 of a 17-year-old patient with severe congenital Factor VII deficiency, who required hysterectomy because of intractable menometrorrhagia, is described. With moderate replacement therapy for a brief time, no excessive bleeding was encountered, which is remarkable in view of the short in vivo survival of Factor VII and the modest rises of Factor VII levels achieved in the patient's circulation. The pertinent literature is reviewed.

CASE REPORT

A 17-year-old female, diagnosed at the age of 4 as having congenital Factor VII deficiency,1 was admitted to the Children's Hospital Medical Center on June 27, 1963, because of uncontrolled menometrorrhagia. Since onset of menarche at the age of 12 she increasingly had menorrhagia, requiring frequent transfusions of blood and bank plasma, which temporarily controlled hemorrhage on each occasion. In October 1959, she was placed on a regimen of progesterone 100 mg. daily for 5 days prior to expected onset of each menstrual period, in an attempt to reduce the amount of bleeding. This was only of temporary benefit. In December 1962, she was started on i.m. injections of medroxyprogesterone acetate (Provera®, The Upjohn Co.) at 5-week intervals and norethindrone (Nor-
lutin®, Parke-Davis) 5 mg. by mouth daily, in another attempt to control hemorrhage. When this failed, she was admitted to the hospital for treatment and evaluation of possible hysterectomy.

The patient's past history is dominated by a life-long bleeding diathesis. After birth, there was abnormally long bleeding from the umbilical cord. Starting at 10 days of age she repeatedly passed bright red blood from the rectum. At 6 weeks of life she was admitted for this reason to the Children's Hospital Medical Center. She weighed 4230 Gm. on admission, Hb was 6.7 Gm. per cent, RBC 2.4 mill./mm.³ Barium enema revealed no abnormalities. Bleeding and clotting times were the only coagulation tests performed at the time and were normal. Following two transfusions of whole blood, consisting of 80 ml. on the day of admission and 60 ml. on the third hospital day, her RBC was 4.4 mill./mm.³. On the fourth hospital day an exploratory laparotomy was carried out in order to investigate the possibility of bleeding from a Meckel's diverticule. No abnormality was found and an appendectomy was performed. There was no excessive bleeding either during surgery or postoperatively. Wound healing proceeded uneventfully and sutures were removed on the sixth postoperative day. Stools continued to be guaiac positive, although no gross bleeding occurred. At the age of 2 months she had another episode of bleeding from the rectum, which did not necessitate transfusion therapy. At 1½ years of age she had a severe epistaxis following a fall on the face; no transfusion was given. She remained essentially well until the age of 3 years and 10 months, when she was readmitted to the Children's Medical Center because of passage of blood by rectum, hematemesis and epistaxis. Bleeding was controlled by blood transfusions. Prior to transfusion a prolonged Quick prothrombin time of 72 seconds (normal control 17 seconds) was found, which did not shorten after a course of vitamin K. Dr. Benjamin Alexander was consulted and made the diagnosis of a deficiency in serum prothrombin conversion accelerator (SPCA, proconvertin or Factor VII). From this time until the age of 10 she was cared for at another hospital. She continued to have epistaxes. At the age of 7 she sustained a chip fracture of the right ankle, subsequently bled into this joint and received plasma transfusions on several occasions. At the age of 10 the patient again came under the care of the Children's Medical Center. She continued to have episodic swelling of the right ankle, for which she received transfusions of bank blood, and such orthopedic measures as joint aspiration and wearing of a bivalve cast. Radiograms revealed gross destructive changes in the right ankle, with irregularity of the surface of the talus and widening of the tibial epiphysis. Also periodic hemorrhages into both knee and elbow joints as well as bleeding from the gums around loose teeth and epistaxes were treated by transfusions of bank plasma. At the age of 10 years a carious deciduous molar was extracted by a dentist without prior administration of plasma. There was continuous oozing of blood and the child was brought to the CHMC emergency room 14 hours after the procedure for treatment. One hundred ml. of bank plasma were infused and the tooth socket was packed with oxidized cellulose (Oxycel®). No further bleeding occurred.

Physical examination on her latest hospital admission revealed a well-developed girl, weighing 49.5 Kg. The left elbow joint was swollen. On rectal examination the uterus was fairly large and the cervix was soft. Detailed coagulation tests on the patient were done on July 26, 1963, 2 weeks after the last plasma transfusion (table 1). They showed characteristic findings for isolated Factor VII deficiency, i.e. a greatly prolonged Quick prothrombin time, a depressed Factor VII-X complex, which in the face of normal Factor X reflected a deficiency of Factor VII, and normal Factors II (prothrombin) and V (proaccelerin). Other tests, dependent on intrinsic thromboplastin formation, i.e., clotting time, partial thromboplastin time, prothrombin consumption test and thromboplastin generation test were normal. The meaning of the moderately prolonged bleeding time was not clear, as it has not been a regular feature of Factor VII deficiency in the past. On admission, the patient received 1000 ml. of bank blood, raising her Hct from 27 to 38 per cent. Menorrhagia stopped for a day, but subsequently reappeared, necessitating another transfusion of 500 ml. of whole blood and 250 ml. of bank plasma on the sixth hospital
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Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>Patient</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass clotting time</td>
<td>15 min.</td>
<td>7 min.</td>
<td>Lee-White,30 modified31</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>2–7 min.</td>
<td>15 min.*</td>
<td>Ivy,32 modified31</td>
</tr>
<tr>
<td>Platelet count</td>
<td>200–370,000/cmm</td>
<td>304,000/cmm</td>
<td>Ottenberg33</td>
</tr>
<tr>
<td>Platelet adhesiveness test</td>
<td>30–68%</td>
<td>44%</td>
<td>Salzman,34 modified</td>
</tr>
<tr>
<td>Quick Time</td>
<td>11–14 secs.</td>
<td>86 secs.</td>
<td>Quick,35 using human brain thromboplastin</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>60–100 secs.</td>
<td>90 secs.</td>
<td>Rodman36</td>
</tr>
<tr>
<td>Prothrombin consumption test</td>
<td>85–100%</td>
<td>96%</td>
<td>Quick,37 modified31</td>
</tr>
<tr>
<td>Thromboplastin generation test</td>
<td>9–11 secs.</td>
<td>10.0 secs.</td>
<td>Biggs,38 modified31</td>
</tr>
<tr>
<td>Factor II (prothrombin)</td>
<td>60–170%</td>
<td>58%</td>
<td>Owren,2 modified30</td>
</tr>
<tr>
<td>Factor V (proaccelerin)</td>
<td>60–150%</td>
<td>100%</td>
<td>Owren2</td>
</tr>
<tr>
<td>Factors VII–X complex</td>
<td>60–140%</td>
<td>20%</td>
<td>Owren2</td>
</tr>
<tr>
<td>Factor VII</td>
<td>60–170%</td>
<td>&lt;1.5%</td>
<td>Owren,2 modified30</td>
</tr>
<tr>
<td>Factor X</td>
<td>50–120%</td>
<td>86%</td>
<td>Bachmann40</td>
</tr>
<tr>
<td>Factor VIII (AHF)</td>
<td>50–170%</td>
<td>120%</td>
<td>McMillan31 modified</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>230–490 mg. %</td>
<td>322 mg. %</td>
<td>Ratnoff41</td>
</tr>
</tbody>
</table>

†As the deficient substrate, the asbestos-filtered beef plasma is substituted by a mixture in equal parts of plasma from our patient and barium sulfate-adsorbed oxalated beef plasma.

day, with again only temporary benefit. The patient was very much depressed by the recurrent menorrhagia and by the limitations which it imposed on her activity. Because of persistence of bleeding, hysterectomy was finally carried out on the fourteenth hospital day. In preparation for surgery one unit of blood was withdrawn from the patient. The red blood cells were separated by centrifugation and returned to her together with 500 ml. of bank plasma between 9:00 and 10:30 a.m. This raised Factor VII from less than 1 per cent to 18 per cent with a reduction of the Quick Time from 143 to 18 seconds. During the next 30 minutes another 250 ml. of bank plasma were infused. Forty-five minutes after completion of the infusion, at 11:45 a.m., surgery was begun. At this point Factor VII was 11 per cent and the Quick Time 22 seconds. A supracervical hysterectomy was performed. Apart from momentary brisk bleeding at the time of the skin incision, no abnormal bleeding was encountered during the procedure. About 200 ml. of whole blood were transfused during surgery as a replacement of estimated blood loss. The uterus was slightly enlarged and boggy, the ovaries were unremarkable. Because of the well known quick regression in vivo of Factor VII, infusions of bank plasma during the postoperative period were given at 4-hourly intervals, 200 ml. at a time. Minimal levels of Factor VII varied between 7 and 4 per cent with corresponding Quick Time values between 24 and 30 seconds. Maximum levels were between 14 and 7 per cent with corresponding Quick Time values between 19 and 23 seconds. A constant downward trend of the levels over a 2-day period was observed, and this was thought to be the result of gradual dissipation of Factor VII following the initial loading dose immediately prior to surgery. Graphic presentation of these values is omitted because of the limited number of samples that could be obtained in this patient, who presented particular psychological difficulties. Following the last dose of bank plasma during the forty-fifth postoperative hour, regression of Factor VII was followed at 2-hourly intervals for a period of 8 hours. During the first 4 postinfusion hours Factor VII decreased from 10 per cent to 3.5 per cent; 4 hours later the level was 2.4 per cent. The regression curve did not allow for accurate determi-
nation of the half-life, because levels were not high enough. On a previous occasion, in June 1961, while the patient was not bleeding, the disappearance rate of Factor VII was measured after a single infusion of barium sulfate eluate, which raised the level to 43 per cent. Factor VII disappeared thereafter according to a half-life of 130 minutes. Postoperative vaginal oozing was less than would have been expected from a normal patient undergoing the same procedure and there was no bleeding from the incision wound. Sutures were removed on the seventh postoperative day, and the patient was discharged the next day.

REVIEW OF LITERATURE

Factor VII and Factor X (Stuart-Prower Factor) share certain properties: they are both stable in vitro; deficiency of either results in prolongation of Quick's prothrombin time; they are both adsorbed by barium sulfate or aluminum hydroxide; and they are not consumed during the coagulation process, hence their activity is retained in serum. A deficiency of either is suggested when a prolonged Quick Time is corrected by admixture of normal plasma or serum, but not by admixture of adsorbed plasma or serum. Case descriptions of congenital Factor VII deficiency started to appear in 1951, after the existence of this clotting factor had been previously postulated. With discovery of Factor X in 1956, certain properties differentiating Factor X from Factor VII became known, and reevaluation of previously diagnosed cases of congenital Factor VII deficiency became necessary. It is now generally accepted, that the role of Factor VII is limited to the "extrinsic" coagulation system, whereby clotting is mediated through the action of tissue thromboplastin, whereas Factor X functions in the "intrinsic" coagulation system, in which clotting is accomplished by evolution of plasma thromboplastin. As a consequence the only abnormal coagulation tests in Factor VII deficiency are those in which tissue thromboplastin is used, as in Quick's prothrombin time. Other tests, dependent on plasma thromboplastin formation, as the whole blood clotting time, recalcification time, partial thromboplastin time, prothrombin consumption test, and the thromboplastin generation test, are normal. Some or all of the above tests are abnormal, however, in Factor X deficiency. In addition, coagulation, when mediated by Russel viper venom as a source of thromboplastin, is prolonged in Factor X deficiency, in contrast to Factor VII deficiency. Of the cases of congenital Factor VII deficiency reported to date, satisfy these diagnostic criteria. Aside from hemorrhage attending surgery, bleeding manifestations consisted primarily of epistaxes, bleeding from the gums, menorrhagia, and mild hemarthroses. Umbilical bleeding occurred in some cases during the newborn period. Gastrointestinal bleeding and intracranial hemorrhage were prominent in some infants, causing death in several of them. Nine of 16 postpuberal females suffered from menorrhagia. Two women underwent hysterectomy, one because of menorrhagia, the other because of the existence of fibroid tumors. Two sisters were radiocastrated in their teens because of menorrhagia. True assessment of Factor VII, expressed in percentage of average normal, requires the use of a substrate plasma, severely deficient in only this factor. There is at the present no artificial medium that can serve the purpose and
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one is dependent on the use of plasma derived from a congenitally deficient human or animal. True Factor VII levels measured in this fashion were uniformly below 3 per cent of normal in the reported cases of congenital Factor VII deficiency, who had hemorrhagic diathesis. The method employing asbestos-filtered beef plasma, measures both Factors VII and X (Factor VII-X complex), and generally yielded falsely high levels (4-25 per cent of normal). Plasma obtained after 24-48 hours of treatment with a coumarin drug has also been used as the deficient substrate, and is not quite satisfactory, as it is also relatively deficient in Factor II (prothrombin) and Factor X.

Family studies have shown the disease to be inherited by an autosomal recessive mode. Heterozygotes are asymptomatic and show low normal or slightly reduced levels of Factor VII. Of the 46 described cases of congenital Factor VII deficiency, 21 are recorded as having had surgery. In certain instances surgical procedures, dental extractions in particular, were followed by excessive bleeding for several days, when no transfusions of blood or plasma were given. Two women had excessive postpartum hemorrhage. Another patient, however, delivered three times without excessive bleeding. All patients who were given transfusions of blood or plasma in connection with surgery had no undue bleeding. These were usually single transfusions just prior or during surgery and apparently were not extended to the postoperative period. It is noteworthy that complete hemostasis was achieved in these cases in the face of a very brief in vivo survival of Factor VII, with a “half-life” of 2-6 hours. Despite a history of hemorrhagic diathesis some patients underwent such surgical operations as repair of umbilical hernia, appendectomy, dental extraction, or a “minor operation” without transfusions and had no bleeding difficulties. Two patients without hemorrhagic diathesis received blood transfusions in connection with major surgery for reasons unrelated to any coagulation defect, and surgical hemostasis was undisturbed. They both suffered thrombophlebitis postoperatively and severe deficiency of Factor VII was discovered accidentally when anticoagulant therapy was initiated.

DISCUSSION

Owren’s early statement that Factor VII “has to be reduced to a very low level to give clinical symptoms of hemorrhagic disease,” has been amply confirmed since all symptomatic cases of congenital Factor VII deficiency had Factor VII levels of less than 3 per cent whenever a true assay was performed. Clinical experience with patients under treatment with coumarin derivatives, which suppress production of Factor VII and other clotting factors, as well as assessment of the patients’ bleeding tendency by employment of the primary and secondary bleeding time of Borchgrevink, have led Owren to conclude that Factor VII deficiency was responsible for bleeding tendency only when levels were below 5 per cent of normal. This fact has also to be taken into consideration in other acquired conditions that may be associated with reduction of Factor VII, such as liver disease, vitamin K deficiency and
salicylate intoxication. It is necessary to employ a true assay of Factor VII in order properly to evaluate whether a certain deficiency in Factor VII is of hemostatic significance. An assay method measuring Factors VII-X complex yields levels which are intermediate between individual true levels of Factor VII and X, and therefore in isolated Factor VII deficiency Factors VII-X complex values are significantly higher than the true levels of Factor VII. If another known severely Factor VII-deficient plasma is not available, one can use the patient's own plasma as the deficient substrate for determining the degree of the deficiency in percentage of normal,\textsuperscript{12,16,19,26} provided the defect is severe and limited to Factor VII. Such an assay procedure reveals only the degree, not the nature of the deficiency; the latter is determined by the various qualitative tests mentioned above.

Patients with congenital Factor VII deficiency, who underwent surgery, generally fared well with only shortlasting replacement therapy in moderate amounts. The laparotomy in the patient reported here was undisturbed by hemorrhage, 2 transfusions of whole blood having been given within 3 days prior to surgery. Bleeding for 14 hours following a tooth extraction, performed without replacement therapy, was quickly controlled by local pressure and infusion of a small amount of bank plasma, which could not have raised the level of Factor VII by more than a few per cent. During hysterectomy Factor VII level in our patient was below 11 per cent. As a precaution she was kept on replacement therapy for 48 hours postoperatively, achieving levels between 4 and 10 per cent. However, it appears retrospectively that an earlier cessation of plasma therapy would not have been harmful. Utilizing the data in the literature and our own experience it seems reasonable to prepare a patient with congenital Factor VII deficiency for surgery by infusion of bank plasma, 10 ml. per Kg. body weight, immediately prior to the procedure. The use of fresh or freshly frozen plasma is not necessary because of the in vitro stability of Factor VII. Maintenance therapy, at a safe rate of 4 ml. per Kg. every 4 hours, probably does not have to be extended beyond the first postoperative day. Concentrates of Factor VII\textsuperscript{17,42,59,60} seem dispensable, as effective replacement therapy without danger of circulatory overloading can be easily given with the use of bank plasma.

In Factor VII deficiency requirements for replacement therapy under circumstances of surgery are obviously little in comparison, for instance, to the more common condition of classic hemophilia (hemophilia A). This is all the more remarkable when contrasting the very short in vivo survival of Factor VII (half-life 2–6 hours) with the one of Factor VIII (antihemophilic factor or AHF), which has an average half-life of 14 hours.\textsuperscript{61} Not only are high Factor VIII levels (in excess of 30 per cent) required for surgery in classic hemophilia, but high levels have to be maintained for the whole period of wound healing, in order to prevent secondary hemorrhage.\textsuperscript{31,62} Factor VII, functioning in the extrinsic coagulation system, as mediated by tissue thromboplatin, apparently plays only a brief role in normal surgical hemostasis, perhaps at the time when extravasated blood comes in contact with the surrounding tissue.\textsuperscript{5,8,13} By quick evolution of thrombin, through the action of tissue
thromboplastin, Factor VII may also enhance the development of viscous metamorphosis of platelets which is said to be thrombin-dependent. Non-involvement of Factor VII in the intrinsic coagulation system is also highlighted by the occurrence of postoperative thrombophlebitis in two patients with severe congenital Factor VII deficiency.

SUMMARY AND CONCLUSIONS

Experience with surgery in a patient with congenital deficiency of Factor VII (SPCA, proconvertin) is presented and the pertinent literature reviewed. Factor VII deficiency is not associated with a bleeding tendency, unless levels are lower than 5 per cent of normal, as measured by a true assay. Factor VII levels between 5 and 10 per cent of normal, easily achieved by infusions of bank plasma, appear adequate for hemostasis during surgery. No replacement therapy seems necessary beyond the first postoperative day.

SUMMARIO IN INTERLINGUA

Es describite le experientia colligite in le tractamento chirurgic de un patiente con carentia congenite de factor VII (proconvertina, accelerator seral del conversion de prothrombina). Le pertinente litteratura es revistate. Carentia de factor VII non es associate con un tendentia sanguinatoni si su nivello remane supra 5 pro cento del norma secundo un ver essayage. Nivellos de factor VII de inter 5 e 10 pro cento del norma pare esser adequate pro le hemostase necessari durante un operation. Tal nivellos es facilmente attingite per le infusion de plasma de banca. Nulle therapia de reimplaciamento pare esser necessari in ultra del prime die post le operation.

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HERBERT S. STRAUSS


Herbert S. Strauss, M.D., Assistant in Hematology, Children's Hospital Medical Center; Research Associate, Harvard Medical School, Boston, Mass.
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HERBERT S. STRAUSS