Hemophilia is a genetic disorder which, if poorly controlled at the time of surgery, may create problems for the nurse anesthetist. The authors present an overview of the disorder including its genetic relationships, treatment, anesthetic management, and pain control.

Hemophilia is among the oldest described genetic disorders for which genetic counseling was outlined. The most famous case can be traced back to Alexis, son of Alexandra and Czar Nicholas II of Russia. The etiology of the disorder was poorly understood until 1936, when Patek and Stetson showed that the abnormality lay in the plasma of the patients.\(^1\)

The disorder is transferred from parent to child through the X chromosome. A normal female has two X chromosomes and a male has a Y and an X chromosome. The Y chromosome (the male sex chromosome) has very few genes, while the X chromosome has many. Because of the relative lack of genes in the Y chromosome and the absence of alleles which balance genes of the X chromosome, males are more susceptible to some genetic conditions that do not usually affect females.\(^2\) The classic example of an X chromosome-linked recessive defect is the linking of an affected X chromosome of the mother with the Y chromosome of the father, producing a male child with hemophilia.

### Types of hemophilia

The most severe type of hemophilia is *Hemophilia A*, which is characterized by a marked Factor VIII deficiency. Its frequency is approximately ten times that of the other types of the disorder. The classical episodes of spontaneous bleeding into muscles and joints occur only in those patients who have less than 1% the normal amount of Factor VIII in their plasma.\(^3\)

Christmas disease, or *Hemophilia B* is also inherited as an X-linked recessive trait, characterized by a deficiency in Factor IX. It is distinguished from Hemophilia A only through clotting factor assays and coreaction tests with serum and plasma.

The least severe type of hemophilia was defined by Von Willebrand in 1926, as a hereditary bleeding disorder characterized by epistaxis, skin and mucosal hemorrhage. He described it as being manifested by males and females in whom the coagulation time is normal, but the bleeding time is prolonged.\(^4\) As in Hemophilia A, patients with Von Willebrand's disease have a Factor VIII deficiency.

Through genetic counseling, families can now obtain guidance in accepting and coping with this disorder. The first step begins with a complete family history of both parents, since each can be a carrier. Laboratory tests may reveal the female carrier to have a prolonged coagulation time; the male carrier will demonstrate marked symptoms,
depending on the type of disorder. The information from such testing can aid a couple in making a decision on whether or not to have children, since a known carrier has a 50% chance of having a daughter that will be a carrier and a son that will have the gene and so be affected by the disorder.

The child born with hemophilia faces a life of hidden dangers. A slight bump of the knee can cause bleeding into the joint, swelling, and extreme pain. Other complications include renal obstruction from clots, neurological deficits resulting from head trauma, and psychological problems which can be produced from an “over protective” environment.

With the information provided thus far, it should be apparent that the diagnosis, treatment, perioperative management, and pain control are of great importance when dealing with the hemophilia patient.

**Treatment of hemophilia**

Increasing knowledge of hemophilia pathophysiology has brought a degree of sophistication to its treatment. Early therapy consisted of supportive measures: the application of ice and pressure, plus the transfusion of whole blood, which provided the necessary clotting factors to aid in the control of major hemorrhage. The necessity of ensuring a compatible donor, and the risks of sensitization, hepatitis, and volume overload made whole blood use somewhat dangerous.

Plasmapheresis, the division of plasma from the red blood cells, then became the therapy of choice, but the volume needed for effective treatment was still too large. Even with the development of fractionation, the division of plasma into fibrinogen, Factor VIII, Factor IX and gamma globulins, therapy still could produce transfusion reactions and a possible increase in antihemophiliac factor (AHF) inhibitors, coupled with some loss of Factor VIII during the fractionation process.4

A means of preparing these patients for surgery also was necessary, but there were many drawbacks to the traditional methods. A method of plasma exchange, essentially a double plasmapheresis, helped prevent overload and AHF inhibitor activity by exchanging the recipient’s plasma with that of a compatible donor. It was found that chronic plasmapheresis boosted the effect of the AHF and Factor VIII concentrates, which greatly reduced oozing both intra- and post-operatively.5 However, this method was still not suitable for chronic treatment, since type specific donors were needed and unnecessary fractions were still administered.

Cryoprecipitation opened a new therapeutic world for the hemophiliac. In making this Factor VIII concentrate, plasma is quick frozen within a few hours of donation. The cryoprecipitate remains as a thread-like material after the plasma is thawed. Three milliliters of a pasty material are obtained after centrifuge. When reconstituted with normal saline, this can be given to any blood group.5

All desired fractions are present, principally the so called cold insoluble globulin (CIG) and fibrinogen, as well as Factors VIII and XI and small amounts of plasma proteins.6 This therapy also has the advantage of posing less risk of hepatitis transmission compared to fractionated, pooled products. In addition, with the administration of epinephrine and/or through physical or emotional stress, the Factor VIII content of the donor can be elevated.7,8,9

Of course, there are complications associated with this therapy. Febrile and allergic reactions to white blood cell antibodies, anemia with or without hemolysis, leucocytosis, paradoxical bleeding, liver abnormalities and splenomegaly have all been reported in hemophiliacs. It is believed that these reactions are due to early sensitization from previous transfusions.

There are many debates about the regimental handling of the hemophiliac. Chronic versus acute therapy has been widely discussed. Cryoprecipitate can
be freeze dried, which increases its usefulness in home therapy. For children, with their tendency for accidental injury, such home therapy is ideal, because with a decrease in hemorrhagic episodes, there follows a decrease in synovitis and bone destruction. However, as it takes 1,000 donors to maintain one hemophiliac for one year at immeasurable cost, such prophylactic treatment becomes unrealistic for most of these children.

Preoperative management of the hemophiliac

With continued progress in the understanding of the factors involved in the coagulation of blood, in the control of hemorrhage during surgery, and in the availability of factor concentrates, the management of the hemophiliac patient undergoing surgery has become much easier. However, certain requirements must be met before surgery is undertaken. Prior to the hemophiliac patient undergoing surgical procedures, the following laboratory tests should be performed: (1) a complete coagulation test, (2) an incubated test for factor inhibitors, (3) a complete blood count, platelet and reticulocyte count as well as red cell type.

The replacement factor dosage is calculated on the basis of patient weight and plasma volume which is approximately 40 ml per kg of body weight. One international unit (IU)—which equals the clotting activity found in 1 ml of fresh plasma—of Factor VIII per kg of body weight will raise the plasma level 2%. One IU of Factor IX per kg will raise the level 1-1.5%. To further assist in dosage calculation, factor assays of the patient’s plasma should be done daily prior to administration.

On the morning of surgery, the patient should receive enough factor concentrate to raise the plasma level to 100%. Postoperatively, the patient should be studied to determine the success of the infusion and the amount lost via surgical bleeding. The plasma level of Factor VIII or IX should be maintained at 60% for four postoperative days; and for major surgery, the level should be maintained at 40% for an additional four days.

Knowledge of the half-life of these components, which is 12 hours for Factor VIII and 24 hours for Factor IX, is critical to the decision as to the quantity required for the next dose to attain adequate hemostatic levels. The aim is for infusions at 12-hour intervals.

Clearly, extreme care should be exercised in the preoperative preparation of hemophilia patients. Meticulous attention must be paid to avoiding even minimal trauma. Subcutaneous or intramuscular injections, as routes for preoperative medication, should be performed with extreme care. Diazepam given orally 1½ to 2 hours prior to surgery produces effective sedation and should be satisfactory in most patients.

In the emergency or highly nervous patient, the intravenous route is preferred, thereby expediting sedation. However, as hemophiliacs require repeated intravenous infusions throughout the course of their lives, their veins should be conserved if possible. Venipuncture should be carried out with extreme care and only by those with experience.

For the simple, short procedure, intravenous ketamine is a consideration. For other procedures, an inhalation technique (with care given to protect the lips, tongue, and pharynx from damage by mask pressure), is satisfactory. If endotracheal intubation is necessary, it should be performed with extreme care and gentleness, using a curved laryngoscope blade to avoid epiglottic trauma, and a small, well-lubricated tube. The jaw muscles should be fully relaxed before attempting intubation.

The oral route should always be the first choice, as even the gentlest nasotracheal intubation may cause bleeding. Extubation should be performed with the same gentleness and in a moderate plane of anesthesia to ensure a tranquil emergence. Blind oropharyngeal suction should be avoided; oral
secretions should be removed under direct vision, by gentle suction, never permitting mucosa to be pulled into the suction tip. Extravasation of blood with hematoma formation in the tongue, floor of the mouth, and tissues around the pharynx, larynx and trachea can produce gross swelling, thus, dangerously compromising the airway.16

Local infiltration and regional anesthesia are not recommended in these patients because of the possibility of producing hematoma.16 Spinal and epidural anesthesia could be hazardous because of possible hemorrhage and hematoma formation with neurologic sequelae.

The hemophiliac and pain

Pain in the hemophiliac is divided into three types: (1) that which is due to acute pressure of a hematoma on a sensory nerve, (2) the chronic rheumatoid-like pain secondary to repeated hemarthroses, and (3) the general type, common to everyone, such as, headache and neuralgias.16

In many cases, transfusion of fresh frozen plasma not only brings hemorrhage under control, but also exerts a strong analgesic effect. It is probable that cryoprecipitate has a similar effect which may or may not be due to its content of Factor VIII. Pain associated with rapid hemorrhage into a confined tissue space is decreased or abolished within minutes of achieving hemostasis either by infusion of fresh frozen plasma or factor concentrates.

Continuation of pain after infusion therapy is not an indication for the use of analgesics, but rather is an indication of inadequate hemostasis requiring further intravenous therapy. The use of analgesics for pain following rapid hemorrhages can lead to a delay in recognizing the ineffective arrest of hemorrhage by masking the pain associated with the hematoma formation.

Hemophiliacs constitute a group of patients whose disease makes them more likely than other people to abuse analgesics. One problem in pain control of hemophiliacs is to find a suitable analgesic.

There is an ever-increasing list of analgesics containing aspirin and antihistamines which are known to inhibit platelet aggregation and prolong bleeding time. Patients should be cautioned against the use of any medicine containing aspirin compound, such as Bufferin®, Anacin®, Empirin®, Percodan® and Alka Seltzer®. Recommended alternatives include acetaminophen, propoxyphene, pentazocine, codeine, and meperidine.18

Some hemophiliacs use acetaminophen for pain relief, but many find it inadequate. It is not certain whether or not acetaminophen may cause renal papillary necrosis and acute liver necrosis if taken in quantity.

The corticosteroids have been used for their anti-inflammatory effects in the acute hemarthrosis and chronic synovitis of hemophilia. Indomethacin and phenylbutazone are excellent drugs for arthritis pain, but are potentially harmful for the hemophiliac because of their inhibition of platelet function. Ibuprofen (Motrin®), the newest drug for arthritis pain, is a known prostaglandin inhibitor; for this reason, it is not recommended for the treatment of hemophilia.

An antifibrinolytic agent, epsilon-amino-caproic acid (EACA or Amicar®) has been used on a trial basis to prevent spontaneous bleeding and for dental extractions both in the United States and Europe. The results were unimpressive when Amicar® was used to prevent joint hemorrhages, but promising when used for dental extractions and mouth bleeding episodes. Amicar® has not been advocated in the treatment of hemarthroses, since a clot formed with the drug may not dissolve for many months and may contribute to further joint destruction.18

Conclusion

Hemophilia, which is a disorder of the clotting factors VIII and IX, can now be treated with relative ease.
Knowledge of the genetic processes involved and genetic counseling have aided in a better acceptance of the disorder. Through the efforts of modern research, the problems previously associated with pain control and anesthetic management have largely been eliminated.

REFERENCES

AUTHORS
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