HEPARIN ADMINISTRATION*

METHODS AND RESULTS IN THIRTY CASES

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During the past two years, 30 patients have been treated by general heparinization in the Henry Ford Hospital. In a previous paper,\(^1\) the results in the first 11 cases were presented, a résumé of the history of heparin was given, and the various indications for heparin therapy were discussed. The literature on the subject of heparin has become large, as will be seen from the bibliographies appended to the review by Mason\(^2\) and the monograph by Jorpes.\(^3\) The largest clinical experience has been that of Murray\(^4\) and others, at Toronto, where more than 700 patients have been treated with the material.

In this series of 30 cases, heparin was administered for the following conditions: (1) Postoperative embolism which was not immediately fatal, 24 cases; (2) embolism of a peripheral artery with embolectomy, three cases; (3) luetic thrombosis of the posterior tibial artery, one case; (4) hemiplegia from occlusion of the common carotid artery, one case; and (5) phlebitis, one case.

The gross results will be summarized at this time. Twenty-two of the 24 embolism patients recovered. The two deaths will be analyzed below; one of them apparently represents a failure of heparin in the dosage employed to prevent the recurrence of embolism. The circulation was restored to the legs in two of the embolectomy cases; the third lived only a few hours after an attempted removal of clots from the femoral artery. No flow of blood was obtained, and the grave condition of the patient, who was in the terminal stages of arteriosclerotic heart disease and appeared to have mesenteric embolism also, caused the operative interference to be interrupted without an abdominal approach to the iliac artery. A gratifying result was obtained in the case of luetic thrombosis of the posterior tibial artery,\(^1\) and the one case of phlebitis showed transient amelioration. The patient with hemiplegia from occlusion of the common carotid artery was not benefited by heparinization, and expired.

The general plan of heparin treatment is to elevate the clotting time of the blood to an arbitrary optimum level, in the hope that dangerous clotting may be inhibited. The usual method is to administer the material in a continuous intravenous drip. Under ideal circumstances, this results in a prolongation of the clotting time which neither goes far above nor far below the optimum level. Chart 1 shows what might be termed an ideal heparin

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reaction, with the clotting time being kept at approximately 15 minutes (capillary blood in capillary tubes) by the administration of slightly more than 1,000 units of Connaught heparin per hour. The term “2 per cent solution” on the chart indicates that one 10 cc. vial of heparin was added to each 500 cc. of physiologic saline solution. One hundred milligrams of crystalline heparin is contained in each 10 cc. vial. Hence, the patient received about 1,200 cc. of physiologic saline solution daily.

Chart 2 is included to show two things: first, the results of a clinical trial of a brand of heparin prepared in this country (Liquaemin, Roche-Organon); and second, the effect of intermittent injections of the undiluted material. At that time, Liquaemin was marketed in 5 cc. vials, containing 10,000 units, but this unit is of a potency of only one-fifth that of Connaught heparin. Therefore, five vials (25 cc.) of this material were needed to produce the effect of one 10 cc. vial of Connaught heparin. Recently, Liquaemin has been dispensed in a 10 cc. vial containing 100 mg. of heparin.

Chart 2 also illustrates the effect of intermittent injections at intervals of three hours. McClure and I¹ showed that it was possible to do this without dangerous bleeding. The case reported developed embolism after prostatectomy, and received a course of heparin by the usual continuous intravenous route. Five days after the heparin was discontinued, he had a second small embolism. On account of the presence of mild cardiac decompensation, it was deemed inadvisable to give any saline solution intravenously, and the patient was given the undiluted material, in the amount of 4 cc. of Connaught heparin every three hours. The clotting time was frequently over an hour,
returning to 15 minutes or below in the three-hour period. This method is of value in the last few days of any course of heparin treatment, when it is advisable to have the patient get out of bed and walk without being encumbered by the intravenous apparatus.

Chart 3.—Chart of patient treated with Liquaemin, with parallel clotting time determinations by three methods.

Chart 3 illustrates one of the problems in heparin treatment, namely, the problem of clotting time methods. This is the chart of a patient who was treated with Liquaemin for a period of eight days. During the time when he was receiving the material by continuous intravenous drip, the clotting time was taken at intervals by three methods; namely, venous blood in test tubes, venous blood in capillary tubes, and capillary blood in capillary tubes. It can be seen that the clotting time as measured by the test tube technic was easily maintained at 15 minutes or above by the administration of small amounts of Liquaemin. However, considerably larger quantities would have been necessary to elevate the clotting time to 15 minutes as measured with capillary blood in capillary tubes. Venous blood in capillary tubes occupied an intermediate position. Many of the reports on heparin treatment are not clear on the matter of the clotting time method. In their original directions for heparin treatment, Murray and Best advised that the clotting time be elevated to 15 minutes as measured by the capillary tube method. Recently, Murray states that they are using venous blood in a 1 cc. test tube, with a glass bead for an indicator. The directions accompanying the Liquaemin preparation suggest the use of the Lee and White method, in which venous blood is placed in several test tubes, which are inverted until clotting occurs, the clotting time in the fifth tube being taken as the reading. The determinations on Chart 3 were made with two test tubes. Obviously, reports on heparin treatment should state clearly the clotting time method used, if evaluations of the potency in vivo are to be made. At the present time, no one is willing to state what is the actual optimum clotting time to prevent thrombosis. The expense of heparin is such that one wants to use the least amount that will produce the desired effect. The case report which follows, taken alone, would cause one to try to maintain a clotting time of at least 15 minutes by the capillary tube method.
Case 1.—The patient was an obese woman, age 43. She had drainage of an appendi-
decal abscess of 11 days duration on April 24, 1940. The postoperative course was
stormy, with distention being a troublesome complication. Thus, many factors favoring
embolism were present, namely, several weeks of recumbency in bed, infection, obesity,
and increased intra-abdominal pressure from distention to retard back-flow from the veins
of the legs. On May 25, 1940, one month after operation, and after orders had been
left for her to get up the next day, she had a sudden attack of epigastric pain, sweating
and shortness of breath. The diagnosis of pulmonary embolus was obvious, and heparin
was begun. Large amounts of heparin were necessary to keep the clotting time near
15 minutes (Chart 4). The condition of the patient improved rapidly and heparin was
to be discontinued on June 2, 1940, after one week of treatment. However, at 3:45 A.M.
on this day, she awoke with dyspnea and a hacking cough which was productive of
blood-streaked sputum. The condition of the patient grew steadily worse; there was
marked air hunger and the skin was cold and moist. She was treated with oxygen,
papaverine, morphine, and increased amounts of heparin, but she expired about 24 hours
after the onset of the episode. Postmortem was refused, although it was sought with
great diligence. From clinical examination, death appeared to be due to a second massive
pulmonary embolism. However, acute heart failure could not be entirely ruled out.

Fortunately, an accurate record of the amount of heparin given and the
clotting times had been kept. This record showed that for about two days,
the clotting time was ten minutes, and on one occasion it got as low as six
minutes. Did a clot form during this brief period? Did a piece break off
an old thrombus which had been waving in a large vessel for more than a
week? Regrettably, the answer in this particular case can never be known.
More information was obtained regarding the second fatality during heparin
administration, because an autopsy was obtained.

Case 2.—The patient was a man, age 69, who was admitted to the hospital on the
Medical Service of Dr. Robert Durham. The provisional diagnosis was arterioscle-
rotic heart disease with fibrillation. He had two pulmonary embolisms, thought to have
come from the right auricle, although the presence of femoral phlebitis was discovered
later. He had marked dyspnea, and was heparinized as a last resort. He expired in one
week, with signs of cardiac failure. Autopsy showed huge infarcts of the lungs, which
were thought to be at least one week old. The cardiac muscle showed gross evidence of
degeneration. No hemorrhagic manifestations were discernible.

The complication of hemorrhage has not been prominent in the previous
reports. In 315 cases reported by Murray and Best,7 there were four instances
of hematoma formation in the wound, with the result that heparinization was stopped. Priestly, Essex and Barker noted only transient hematuria a few times in their 45 cases.

In this series, there was hemorrhage from the operative wound four times. Two patients bled from wounds in the popliteal space following embolectomy. Fortunately, the hemorrhage did not begin until four days had elapsed in each case, and the arteries remained patent, even though the heparin was discontinued. The third patient had a rather extensive dissection of the abdominal wall for the excision of a draining sinus. Three days later, he had pain in the chest suggestive of infarction and the next day heparin treatment was begun by the intermittent method, on account of the presence of cardiovascular insufficiency. Four cubic centimeters of Connaught heparin was given every three hours, and the clotting time rose to 20–30 minutes after each injection, the maximum being 46 minutes on one occasion. An hematoma developed on the second day, and the heparin was discontinued, inasmuch as sputum studies indicated that the pain in the chest was due to bronchopneumonia rather than embolism. The fourth patient had pain in the chest on the twelfth day following hysterectomy. Heparin was started, but was given in abnormally large amounts for several hours, with the result that the clotting time was 65 and 75 minutes on two occasions. The patient began to bleed from the vagina after 24 hours of treatment, and this was controlled with some difficulty by stopping the heparin and packing the vagina. One transfusion was given. Recovery was rapid.

There was one case of concealed hemorrhage. A very obese woman, age 42, had a spinal fusion. During the third week of convalescence, she had several small pulmonary embolisms. Heparin was begun, by the use of a continuous intravenous cannula placed in a vein on the medial side of the left ankle. The right leg is usually used for this procedure, on account of the propensity of the left for phlebitis, but in this case a bone graft had been removed from the right leg, so the left was chosen. The clotting time was maintained at the optimum level by giving 1,000 units of heparin per hour (Chart 5). On the third day of treatment, the patient complained of severe

![Chart 5](image-url)

Chart 5.—Heparin chart of patient who developed a massive hematoma in the thigh (Fig. 1).
pain in the region of the femoral vessels of the left leg. The leg was repeatedly examined, and no cause for the pain could be found. Later, she complained of feeling faint. The true state of affairs was not recognized until three days later, when bulging in the left thigh was noted (Fig. 1). The

![Photograph of legs of the patient who developed an huge hematoma in the left leg on the third day of heparin administration.](image)

hemoglobin determination at this time showed 5 Gm., or 33 per cent. It was obvious that the swelling represented a massive hematoma which had come from an unknown source in the leg. It is of interest to note that the vitamin C on the patient this day was 0.20 mg., which is about scurvy level, and there was evidence of capillary fragility by the tourniquet test. Apparently the combination of the two hemorrhagic tendencies resulted in the subcutaneous bleeding.

**Comment.**—It has not been my intention to paint a dark picture for heparin therapy. I have mentioned the complications, having little to say about the other cases who comprise the majority of the series, who had uninterrupted recoveries after having had one, two, and even three previous
HEPARIN ADMINISTRATION

pulmonary infarcts. Heparin has a place in the treatment of thrombosis. Its value in embolectomy and other kinds of blood vessel surgery is even greater. However, those who use heparin should keep in mind such reports as that of Potts, who carried 518 patients through various operative procedures with no clinically recognizable evidence of thrombosis or embolism, by simply making them carry out a simple exercise in bed! Still more puzzling is the report of Reed, who stated that he had deliberately reduced the clotting time in a series of operative cases, by the administration of adrenal cortical extract. He had had no embolism or thrombosis in over 200 cases!

REFERENCES

6 Murray, D. W. G.: Personal communication, October, 1940.