TREATMENT OF MASSIVE HEMORRHAGE IN OBSTETRIC CASES BY TRANSFUSION AND NOREPINEPHRINE *

BERNARD E. CAPPE, M.D., AND IRVING M. PALLIN, M.D.†

Brooklyn, New York

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IN 1910, Barger and Dale suggested that epinephrine and others sympathomimetic pressor amines related to it were released at the sympathetic nerve endings, and that these mediated various physiologic responses (1). In 1946, Von Euler, experimenting with mammals, found a norepinephrine-like substance in various tissues and organs containing adrenergic fibers (2). In 1948, Tainter, Tullar and Luduena were able to resolve arterenol (norepinephrine) and presented a description of the physical and physiologic characteristics of both the levo and dextro isomers (3, 4). Luduena showed that the *l*-isomer was twenty-seven to sixty times more active than the *d*-isomer (5). Tullar, in 1949, reported that he was able to separate the *l*-isomer from several commercial lots of epinephrine and from a sample obtained from bulk, natural U.S.P. epinephrine reference standard (6). Norepinephrine was then shown to occur in considerable amounts in the adrenal medulla and in adrenal medullary tumors (pheochromocytomas) (7, 8).

Hemodynamic studies in man using the method of right heart catheterization and determining cardiac output by the Fick method have shown that epinephrine within a physiologic range acts as an over-all vasodilator and causes hypertension only by increase of cardiac output. Norepinephrine, on the other hand, acts as an over-all vasoconstrictor with no change or slight decrease of cardiac output. This vasoconstrictor action was completely blocked by the synchronous administration of epinephrine (9). Goldenberg, Apgar et al., utilizing patients undergoing the second stage of lumbar sympathectomy, gave *l*-norepinephrine (4 cc. of 1:1000 dilution in 1 liter of normal saline solution) by continuous intravenous infusion. The rate of flow of the solution was adjusted to produce and maintain the desired level of blood pressure and this was accomplished in all but one of 23 cases.

Norepinephrine was similarly given but in slightly higher concentrations to 2 patients, one with severe gastrointestinal hemorrhage

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† Department of Anesthesia, Jewish Hospital of Brooklyn, Brooklyn, New York.

and one with intraperitoneal hemorrhage. In both cases, repeated transfusions of whole blood intravenously had failed to produce significant elevations of the blood pressure which, however, rose to normal values during administration of nor-epinephrine given for one to four hours. Three patients with severe central vasomotor depression were also treated with the *l*-norepinephrine solution; in each the blood pressure was maintained at desired levels (10).

In obstetrics, massive hemorrhage still remains one of the leading causes of maternal death (11). If hemorrhage remains unchecked, there is progression to impending shock, shock and irreversible shock. Of all the measures which have been recommended, the rapid replacement of blood to the circulatory system remains the basis of therapy of hemorrhagic shock. Blood replacement, oxygen administration, intravenous infusion of alkali solution, such as sixth molar sodium lactate, hemostasis and atraumatic operative procedures help reverse the shock mechanism. Although recovery from irreversible shock is impossible by definition, we wish to describe our experience in 3 cases of profound shock.

Case 1.—On May 22, 1950, an elective procedure, a low flap cesarean section, was being performed for the second time on this patient, a 40-year-old gravida II unipara. Difficulty was encountered with the repair of the flap because of constant oozing. Blood oozed from each point pierced by the needle. A supracervical hysterectomy, right salpingo-oophorectomy and left salpingectomy had to be done to control the bleeding. During the latter part of the procedure, the blood pressure dropped to 40 mm. systolic and 30 mm. diastolic and neosynephrine, 1 minim, was given intravenously and repeated in three minutes. There was no change in the blood pressure. Then 4 cc. of 1:5000 *l*-norepinephrine was added to 500 cc. of compatible blood and administered rapidly. The blood pressure returned to a normal level in the next five minutes and was maintained.

After completion of the procedure, oozing persisted from the abdominal incision. A total of 2000 cc. of blood from the blood bank had been given. A diagnosis of hypofibrinogenemia was made and patient then received a transfusion of 1000 cc. of whole fresh blood by the direct method. Three ampules of fibrinogen, dissolved in 5 per cent glucose in water, were given intravenously during the next few hours. The patient had a stormy convalescence but eventually made complete recovery.

Case 2.—This 40-year-old colored, gravida IX, sextipara,delivered spontaneously at 1:50 a.m. on August 23, 1950. On admission, the antepartum blood pressure was 110 mm. systolic and 68 mm. diastolic; on leaving delivery room the blood pressure was 90 mm. systolic and 60 mm. diastolic and the pulse was 96. The patient began to bleed excessively during the next two hours. She objected violently to blood transfusion because of religious scruples. An intravenous infusion of 1000 cc. of 5 per cent glucose in water and 1/320 grain of ergonovine maleate were given. At 3:50 a.m. the fundus was firm and the blood pressure 90 mm. systolic and 50 mm. diastolic. Subsequently, her condition became worse and at 5:45 a.m. no pulse or blood pressure reading was obtainable. Venesection was performed and 500 cc. of plasma, 1000 cc. of one sixth molar sodium

lactate and 1000 cc. of blood were given. At 6:15 a.m., after 500 cc. of plasma and 1000 cc. of blood were given, the blood pressure and pulse were still unobtainable. Four cubic centimeters of 1:5000 *l*-norepinephrine was added to another 1000 cc. of blood and given rapidly. The blood pressure rose to 94 mm. systolic and 60 mm. diastolic in ten minutes but the patient still remained comatose. A rent in the posterior fornix of the vagina was repaired. The blood pressure rose to 105 mm. systolic and 70 mm. diastolic at completion of the second infusion of 1000 cc. of blood. At 8:45 a.m. a further examination of the vaginal canal was made and several superficial lacerations were sutured. Digital exploration of the uterus suggested a rupture of the lower posterior uterine segment. Bleeding became active and the blood pressure reading dropped to 80 mm. systolic and 50 mm. diastolic. At 11:00 a.m. under local and cyclopropane anesthesia laparotomy was performed. When the peritoneal cavity was opened, a massive intra-abdominal hemorrhage of about 3000 cc. of blood was found. There was a rent in the lower posterior uterine segment. During the procedure the patient ceased breathing. Pulse or blood pressure reading could not be obtained. Resuscitative measures were of no avail.

Case 3.—This patient, a 32-year-old gravida III unipara, was delivered by low forceps at 10:02 a.m. on November 6, 1950. Several attempts at modified Credé's expression of the placenta failed and it was manually removed. When she was returned to her room at 11:00 a.m. the blood pressure was 100 mm. systolic and 70 mm. diastolic and the pulse was 104. At 2:30 p.m. the blood pressure was not obtainable. After several unsuccessful attempts to insert a needle into a vein it was cut and 1000 cc. of compatible blood was forced in by positive pressure. Oxygen was given by mask. The pulse and blood pressure were not obtainable. To the next 500 cc. of blood, 4 cc. of *l*-norepinephrine, 1:5000, was added; the transfusion was given rapidly by positive pressure. Within five minutes a blood pressure reading of 85 mm. systolic and 50 mm. diastolic was obtained and the pulse was 120. The rate of administration of the blood was slowed; in the next ten minutes the blood pressure rose to 120 mm. systolic and 80 mm. diastolic and then to 140 systolic and 85 diastolic, with a pulse of 110. At 4:05 p.m. under cyclopropane anesthesia supravaginal hysterectomy was performed. The intraperitoneal cavity contained about 3000 cc. of free blood. On the posterior aspect of the uterus near the left cornua, there was an elliptical rent, 1.5 cm. long, in the serosa. Postoperatively, it was demonstrated that there was no communication between the rent and the interior of the uterine cavity. Recovery was uneventful except for thrombophlebitis of the vein on which the cut was made.

In the second and third case, hemorrhage had produced shock of such severity that pulse and blood pressure readings were not obtainable for thirty minutes or longer. Although an infusion of 1000 cc. of blood was given in less than ten minutes, no blood pressure could be detected. It was only after the administration of the blood containing the L-norepinephrine that the condition of shock began to reverse.

In the second case the blood pressure returned to and was maintained at normal levels. The patient died, however, probably because the diagnosis of ruptured uterus and the decision to operate was delayed nine hours.

An attempt has been made to establish a routine method of therapy for hemorrhagic shock. The control of bleeding and rapid replacement of blood remain as the basis of treatment. Since the intravenous administration of alkaline fluids combats the accompanying acidosis (11), a 1000 cc. of ⅙ molar sodium lactate solution is given in another vein at the time of the administration of blood. Oxygen is given by mask. Theoretically, the administration of oxygen should help combat the tissue anoxia, although its benefit has been challenged by some writers (12, 13). A transfusion of 4 cc. of 1:5000 *l*-norepinephrine mixed with 500 or 1000 cc. of blood is administered rapidly by positive pressure. When the blood pressure reaches normal levels, blood replacement continues more slowly until estimated blood loss is corrected. Theoretically, the addition to the blood of a vasopressor substance such as *l*-norepinephrine should aid compensatory mechanisms to maintain vasoconstriction of the arterioles and dilate the coronary arteries. There is the possibility that *l*-norepinephrine may constrict the arterioles even when compensatory mechanisms are no longer operating.

Since no control studies were made, it cannot be conclusively stated that the *l*-norepinephrine was directly responsible for raising the blood pressure. In each instance blood was given simultaneously with *l*-norepinephrine and it is possible that blood, if given alone, would have improved the circulation. The rapid and marked improvement in each case, immediately after the blood containing the *l*-norepinephrine had been given, however, would lead us to infer that *l*-norepinephrine was helpful.

SUMMARY

The development and actions of *l*-norepinephrine have been briefly reviewed. Three cases of massive obstetric hemorrhage have been presented and the treatment outlined. The results obtained with *l*-norepinephrine are encouraging and warrant further trial.

REFERENCES

1. Barger, G., and Dale, H. H.: Chemical structure and Sympathomimetic Action of Amines, J. Physiol. **41**: 19 (1910).
2. Von Euler, U. S.: Specific Sympathomimetic Ergone in Adrenergic Nerve Fibres (Sympathin) and Its Relations to Adrenaline and Nor-adrenaline, Acta physiol. Scandinav. **12**: 73–97 (1946).
3. Tainter, M. L.; Tullar, B. F., and Luduena, F. P.: Levo-arterenol, Science **107**: 39–40 (Jan. 9) 1948.
4. Tullar, B. F.: Resolution of *d,l*-Arterenol, J. Am. Chem. Soc. **70**: 2067 (1948).
5. Luduena, F. P.; Ananenko, E.; Siegmund, O. H., and Miller, L. C.: Comparative Pharmacology of Optical isomers of Arterenol, J. Pharmacol. & Exper. Therap. **95**: 155 (1949).
6. Tullar, B. F.: The Separation of *l*-Arterenol from Natural U.S.P. Epinephrine, Science **109**: 536 (1949).
7. Goldenberg, M.; Faber, M.; Alston, E. J., and Chargroff, E. C.: Evidence for Occurrence of Nor-epinephrine in Adrenal Medulla, Science **109**: 534 (May 27) 1949.
8. Holton, P.: Nor-adrenaline in Adrenal Medullary Tumors, Nature **163**: 217 (1949).

9. Goldenberg, M.; Pines, K. L.; Baldwine, E. de F.; Greene, D. G., and Roh, C. E.: Hemodynamic Responses of Man to Nor-epinephrine and Epinephrine and its Relation to problem of Hypertension, Am. J. Med. **5**: 792–806 (Dec.) 1948.
10. Goldenberg, M.; Apgar, V.; Deterling, R., Jr., and Pines, K. L.: Nor-epinephrine (Arterenol, Sympathin N) as Pressor Drug, J.A.M.A. **140**: 776–778 (July 2) 1949.
11. Cole, J. T.: Method of Treating Massive Obstetric Hemorrhage, J.A.M.A. **135**: 142–144 (Sept. 20) 1947.
12. Price, P. B.; Richards, R. C., and Hammond, J. B.: Evaluation of Oxygen Therapy, Ann. Surg. **130**: 747–754 (Oct.) 1949.
13. Goodman, L., and Gilman, A.: The Pharmological Basis of Therapeutics, New York, Macmillan Co., 1941, p. 681.