Comparative Study of Polybrene and Protamine for Heparin Neutralization in Open Heart Surgery *

C. WALTON LILLEHEI, M.D., LAURENCE P. STERNS, M.D., DAVID M. LONG, M.D., DERWARD LEPLEY, JR., M.D.**

From the Department of Surgery and Variety Club Heart Hospital, University of Minnesota, Minneapolis

OPEN HEART surgery is rapidly increasing in volume throughout the world. Moreover, extracorporeal perfusion technics are being increasingly employed for treatment of aortic aneurysms, renal failure, and certain types of advanced malignancies. Since systemic heparinization is usually necessary for these procedures, the need for more adequate and efficient drugs for heparin neutralization has become paramount.

Polybrene, a quaternary ammonium salt with the empirical formula $(C_{13}H_{30}Br_2N_2)_x$, has been evaluated for its heparin naturalization effects by Preston and coworkers [6, 7] and subsequently by Weiss *et al.*[8] The latter group compared the effects of polybrene and protamine sulfate in improving the coagulation times of heparinized patients and concluded that polybrene was more effective.

The clinical study herein reported has surveyed the effectiveness of polybrene in 50 unselected consecutive patients upon whom open heart surgery was performed at the University of Minnesota Heart Hospital and compares them to an immediately previous consecutive group of 50 patients in whom heparin neutralization was carried out by means of protamine sulfate, utilizing the quantity of postoperative chest drainage as the principal means for comparison.

* Submitted for publication March 17, 1959.

** USPHS Research Fellowship.

This work was supported by research grants from: 1. The Graduate School, University of Minnesota, 2. Minnesota Heart Association, 3. Life Insurance Medical Research Fund, 4. National Heart Institute, Grant No. 830, 5. Minnesota Cardiovascular Surgical Research Fund.

Experimental Studies with Polybrene

In order to explore any possible or potential sources of complications with the use of polybrene as well as to determine its safety range, a series of animal experiments was carried out. These were planned to determine specifically the acute and delayed effects of rapid intravenous injection of large dosages undiluted into heparinized animals.

Method of Study

Seven mongrel dogs weighing six to 15 kilograms received 1.5 mg. heparin per kg. of body weight. After ten minutes to allow complete mixing of the heparin, polybrene was given intravenously, undiluted (10 mg. per cc.), as rapidly as it could be injected in dosages equal to four, six, and eight times the amount of heparin given. Three dogs received 6 mg. polybrene per kg. of body weight, two received 9 mg. polybrene per kg. of body weight, and two dogs received 12 mg. polybrene per kg. of body weight. The dosage recommended by Weiss and co-workers was 1 mg. polybrene for each mg. of heparin. In the described clinical series, we have generally given polybrene, 2 to 2.5 mg., per kg. of body weight.

Results

No animals were anesthetized, and while no measurements of blood pressure were made, there were no discernible acute sys-

temic effects from this rapid injection of these grossly excessive doses of polybrene.

All animals were then placed in a metabolic cage and urine was quantitatively collected for four days. The amounts were recorded, specific gravity measured, any gross abnormalities looked for, and a complete urinalysis performed on the pooled specimens from each 12-hour collection interval. All of these studies were within normal limits. Blood nitrogen studies were done on one animal in each dosage group pre-injection and 12 hours post-injection and these determinations were all normal. The plasma hemoglobin was measured in each animal immediately after injection and 24 hours later and there were no significant changes found.

Finally, the animals demonstrated no evidence of delayed toxicity and when sacrificed two weeks later there were no gross pathologic changes observed.

Weiss *et al.*[8] have advised that polybrene be administered intravenously slowly (over a 10 to 15 minute interval) and in dilute concentration. This recommendation certainly is a judicious policy with any intravenous medication of a potent nature. The experimental studies herein undertaken and reported are not intended to alter that policy, but rather to provide additional information upon the margin of safety existing. Also, prior to these studies we had raised the question as to whether there might be any danger of intravascular clotting with consequent micro- or macro-embolization, if polybrene was given very rapidly to heparinized patients. This appears to be unlikely from the experimental studies reported.

Method of Clinical Study

Fifty patients had open heart surgery performed between February 17, 1958, and June 23, 1958, and all were treated upon completion of cardiopulmonary bypass, with polybrene to counteract the effects of heparin. The helix reservoir bubble oxygenator and Sigmamotor pump [5] were utilized in all 50 cases.

The preceding 50 patients, operated upon between September 23, 1957, and February 16, 1958, were treated with protamine sulfate to neutralize heparin. Of these, 48 were operated upon utilizing the helix reservoir bubble oxygenator and Sigmamotor pump and in two patients a film type oxygenator with roller pumps was utilized.

In these two groups, the charts were thoroughly reviewed, the patients' ages, weights, and diagnoses recorded. The chest drainage, measured during the first 12 hours, the first 24 hours, and the second 24 hours following surgery, was recorded and the number of cubic centimeters of drainage per kg. body weight was calculated.

In patients who received protamine sulfate, the drug was administered in a dosage of 2 mg. per mg. of heparin given to the patient. The drug was given intraveneously slowly in divided doses to prevent the sequela of hypotension.

Those patients receiving polybrene had the drug administered in a dosage range of 1 to 2 mg. of polybrene per mg. of heparin given to the patient. The drug was diluted to contain 1 mg. per cc. of 5 per cent glucose in water and given intravenously slowly, over a 10-minute period as recommended.[8]

In all patients, heparin was administered intravenously in a dosage of 1.5 mg. per kg. of body weight for infants and children and 2.0 mg. per kg. of body weight for adults.*

* Since submission of this paper we have increased our routine dose of heparin for initial patient heparinization in open heart procedures to 3.0 mg./kg. body weight if the perfusion is deemed likely to last less than 60 minutes and 4.0 mg./kg. body weight for those longer than 1 hour. The priming blood in the oxygenator contains, in addition, 20 mg. heparin per 500 cc. Polybrene is administered on the basis of 4.0 to 5.0 mg./kg. body weight.

TABLE 1. *Diagnosis in the Two Groups of Patients Undergoing Open Heart Surgery and Receiving Polybrene or Protamine for Heparin Neutralization*

Diagnosis	Protamine Administered	Polybrene Administered
Ventricular septal defect	16	27
Atrial septal defect	10	6
Tetralogy of Fallot	12	3
Pulmonary stenosis (infundibular and valvular)	3	7
Mitral insufficiency	5	1
Aortic insufficiency	1	2
Mitral stenosis	1	0
Aortic stenosis	1	0
Atrioventricularis communis	1	3
Left ventricular aneurysm	0	1
Total	50	50

Distribution of Patients

In both groups studied, a variety of congenital and acquired heart lesions were treated by open heart surgery (Table 1) but congenital lesions were predominant. In the polybrene group, 11 were adults and 39 were children and in the protamine group, 19 were adults and 31 were children. The age range in the polybrene group was 2 to 65 years with an average of 13 years. In the protamine group, the range was 2 to 44 years with an average of 15.4 years. The average body weight of those treated with polybrene was 39.5 kg. with a range of 8.8 kg. to 65.8 kg. In the protamine group, the average body weight was 34.1 kg. with a range of 8.8 kg. to 49.4 kg.

Results

In patients having a thoracotomy, whether for a procedure requiring heparinization or not, it has been observed that the chest drainage postoperatively during the first 12 hours will usually be almost pure blood, from 12 to 24 hours sanguineous with a hemoglobin content of 6 to 7 Gm. per cent, and from 24 to 48 hours serosanguineous with an average hemoglobin content of 2 to 4 Gm. per cent.

Chest drainage in the first 12 hours in the 50 patients undergoing open heart procedures who received polybrene to neutralize heparin, averaged 11.34 cc. per kg. of body weight with a range of 3.5 to 25.6 cc. per kg. During the first 24 hours the drainage averaged 16 cc. per kg. of body weight with a range of 7.7 to 33.5 cc. per kg. of body weight. In the second 24 hours in this group, the chest drainage averaged 6.6 cc. per kg. of body weight with a range of 1.7 cc. to 22.8 cc. per kg. body weight.

In the group of patients, otherwise similar but who received protamine sulfate, the chest drainage during the first 12 hours averaged 18.04 cc. per kg. of body weight with a range of 5.9 to 55.6 cc. per kg. During the first 24 hours the average was 24.6 cc. per kg. of body weight with a range of 7.5 to 71.3 cc. per kg. of body weight. During the second 24 hours the chest drainage averaged 13.0 cc. per kg. of body weight with a range of 1.0 to 42.7 cc. per kg. of body weight. These results for the two groups are summarized in Table 2.

These comparative results may also be expressed in another way. In the group which received protamine, 64 per cent of the patients had an average chest drainage of 20 cc. per kg. of body weight or less in the first 12 postoperative hours, 52 per cent in the first 24 hours, and 62 per cent in the second 24 hours. Moreover, 84 per cent of the protamine-treated patients had 30 cc. per kg. or less in the first 12 hours and 70 per cent in the first 24 hours.

In the polybrene group, 92 per cent had 20 cc. per kg. of body weight or less in the first 12 hours, 74 per cent in the first 24 hours, and 92 per cent in the second 24 hours. All had 30 cc. or less in the first 12 hours and 94 per cent in the first 24 hours. Thus, in every category the amount of postoperative chest drainage averaged less in the polybrene-treated group.

It is evident from an examination of Table 1 that the diagnoses for which the open-heart procedures were carried out were not strictly comparable in the polybrene- and protamine-treated groups. Therefore, to in-

TABLE 2. *Comparison of Postoperative Chest Drainage in 100 Patients Heparinized for Open Heart Operations and Treated Postperfusion with Polybrene or Protamine Sulfate*

	No. of Patients					
	Polybrene			Protamine		
Chest Drainage (cc./kg. body wt.)	First 12 hrs.	First 24 hrs.	Second 24 hrs.	First 12 hrs.	First 24 hrs.	Second 24 hrs.
0–10	30	12	34	17	12	19
11–20	16	25	12	15	14	22
21–30	4	10	4	10	9	6
31–40	0	3	0	4	7	2
41–50	0	0	0	2	5	1
51–60	0	0	0	2	2	0
61–70	0	0	0	0	1	0
Average range	11.34 (3.5–25.6)	16.00 (7.7–33.6)	6.60 (1.7–22.8)	18.04 (5.9–55.6)	24.60 (7.5–71.3)	13.00 (1.0–42.7)
Total No. of Pts.	50	50	50	50	48	48

vestigate whether this fact might have had any significant influence upon the results obtained, the data for the two commonest lesions (atrial and ventricular septal defects) in the two series was compared in Table 3. Again it may be seen that the postoperative chest drainage for the polybrene-treated patients averaged consistently less.

In the group of patients receiving polybrene, no instance of severe postoperative bleeding occurred causing concern or consideration of return to the operating room for evacuation of clots and further hemostasis.

In the protamine group, two patients died within 24 hours after completion of the surgical procedure. In both of these patients the sustained-bleeding effects appeared to have contributed to the failure to survive.

Case 1, a 14-year-old white boy, deeply cyanotic, who weighed 34.0 kg., was operated upon for repair of severe isolated infundibular and valvar pulmonic stenosis (patent foramen ovale) on December 27, 1957, utilizing the helix reservoir bubble oxygenator. At the time of surgery the right ventricular pressure dropped from 155/0 mm. Hg, before correction, to 60/0 mm. Hg afterwards. He was returned to the recovery room in good condi-

TABLE 3. *Comparison of Heparin Neutralizing Agents Upon Postoperative Chest Drainage in 59 Patients Undergoing Corrective Surgery with the Pump-Oxygenator*

	Average (Range) with Postoperative Chest Drainage (cc./kg. body wt.)			
	Polybrene		Protamine Sulfate	
Diagnosis	12 hrs.	24 hrs.	12 hrs.	24 hrs.
Ventricular septal defect	7.7 (3.4–25.6)	15.4 (4.4–31.8)	12.2 (4.2–24.0)	19.3 (9.8–28.5)
	27 Patients		16 Patients	
Atrial septal defect	12.6 (8.0–19.3)	18.7 (11.5–33.6)	14.5 (7.5–19.3)	21.9 (12.1–32.4)
	6 Patients		10 Patients	

tion but during the next 5 hours 859 cc. of drainage occurred from the chest tubes. The blood loss was continually replaced but he expired suddenly of cardiac arrest at 10:00 p.m. on the day of surgery. Autopsy revealed 600 cc. of blood in the right chest which had not been visualized in a roentgenogram taken within 30 minutes of death.

Case 2, a 5-year-old white girl who weighed 13.1 kg., was operated upon for repair of a ventricular septal defect on January 22, 1958, utilizing a rotating film type oxygenator with nonocclusive roller pumps. The patient entered the recovery room at 3:00 p.m., after an operation which was without incident. By 7:00 p.m. it was noticed that the quantity of bleeding from the chest tubes was definitely abnormal and during the next four hours the patient lost 614 cc. by this route. Fibrinogen and calcium gluconate were given without appreciable benefit. Serial chest roentgenograms at midnight for the first time showed the right chest to contain a significant amount of fluid and shortly thereafter while preparations were being made to reopen the chest, cardiac arrest occurred. The chest was opened and blood replacement and cardiac resuscitation instituted but to no avail. At autopsy, no definite bleeding source could be identified.

Discussion

In these patients the results of the use of polybrene to neutralize heparin have been very satisfactory. The quantity of sanguineous chest drainage postoperatively has been consistently less in the polybrene-treated group. This fact is of importance even when the quantities involved are not excessive because the replacement blood usually available from the blood bank is very acid.* Thus, the administration of blood can be a significant factor contributing to postoperative acidosis when the amounts are large or rapid administration is necessary. Moreover, we have found that the range of bleeding following operation has been narrowed in those receiving polybrene and the occasionally excessive amounts recorded in the protamine group have been generally avoided. Inasmuch as all of these patients were operated upon by the same surgeon using technics that had become generally standardized in 400 similar procedures prior to the onset of this study and, in all but two patients, using the same pump-oxygenator, the results would appear to corroborate completely the conclusion of Weiss, Gilman, Catenacci, and Osterberg [8] that polybrene is a more effective heparin-neutralizing agent than protamine sulfate for patients undergoing open-heart operations.

However, careful analysis of the data herein presented, as well as that of Weiss *et al.,* indicates that there is a wide area of overlap in the effectiveness of these two heparin-neutralizing agents. This observation serves to emphasize that the most important factor of all in minimizing postoperative bleeding in perfusion patients is meticulous hemostasis. Of importance, also, are a number of factors previously emphasized related to the extracorporeal circuit through which the blood may circulate for long intervals such as carefully designed adaptors, connectors, and filters,[2, 4, 7] disposable heat sterilizable plastic oxygenators and tubing,[5] and thoughtfully designed and adjusted pumps.[3] Moreover, the choosing of blood donors and cross-matching technics is worthy of more attention than is sometimes exercised in nonperfusion operations to avoid incompatibility reactions.

With attention to these factors, bleeding following systemic heparinization for open-heart surgery has not been a common problem in our experience. However, the occasional individual who bleeds in abnormal amounts following operation poses a very serious problem, and a few words about management are indicated here. The natural tendency under these unpleasant circumstances is to procastinate in the hope that the losses will slacken. However, to do this is to court disaster from a number of sources, such as metabolic acidosis, citrate intoxication, shock, inadequate ventilation, respiratory acidosis, and cardiac arrest. The most effective treatment, as we have previ-

* The usual banked venous blood stored in acid citrate dextrose solution often has a pH of 6.8 to 7.0.

ously sought to emphasize,[1] is the return of the patient to the operating room as soon as the excessive bleeding has become evident, and while his clinical condition is still good, reopen the chest, evacuate the clots, and locate the bleeding sources.

Since the conclusion of this clinical study, we have continued to use polybrene exclusively and our experience with it now exceeds 400 patients. The benefits of polybrene have been particularly noticeable in two types of patients rather commonly encountered; namely, those with extensive intrathoracic adhesions, either from previous surgery or from inflammatory episodes, and in the deeply cyanotic individuals with markedly abnormal clotting mechanisms. With due attention to the other factors already mentioned these patients can be heparinized and perfused for periods exceeding two hours in our experience, with complete freedom from concern about excessive postoperative bleeding.

Summary

1. One hundred consecutive unselected patients, upon whom open-heart surgery had been performed by perfusion technics, had heparin neutralization with protamine sulfate and polybrene (50 patients each).

2. Evaluation of the chest drainage during the first 12-hour periods revealed an average of 11.34 cc. per kg. of body weight in those treated with polybrene and 18.04 cc. per kg. in those treated with protamine.

3. Ninety-two per cent of the patients treated with polybrene had chest drainage of 20 cc. per kg. of body weight or less during the first 12 hours; whereas only 64 per cent of those treated with protamine had drainage below this amount.

4. No single case of hemorrhage following open-heart surgery caused death or the necessity of returning to the operating room for further hemostasis, in the 50 patients treated with polybrene. In the group treated with protamine two patients died, and in both of these, hemorrhage was thought to have contributed importantly to the cause of death.

5. These studies indicate that polybrene is a more effective agent than protamine sulfate for neutralization of heparin following open-heart surgery. However, it is important to emphasize that no heparin-neutralizing agent, presently known, will compensate for deviations from meticulous hemostasis and carefully designed, heat sterilized disposable perfusion equipment for handling the extracorporeal blood flow.

Acknowledgment

We wish to acknowledge the assistance of Dr. A. E. Osterberg of Abbott Laboratories, Chicago, Illinois, in supplying the polybrene used for this evaluation.

References

1. Barnard, C. N., R. A. DeWall, R. L. Varco and C. W. Lillehei: Pre- and Postoperative Care for Patients Undergoing Open Cardiac Surgery. Dis. Chest, **35**:194, 1959.
2. DeWall, R. A., H. E. Warden, R. L. Varco and C. W. Lillehei: The Helix Reservoir Pump-Oxygenator. Surg., Gynec. & Obst., **104**:699, 1957.
3. Hodges, P. C., R. H. Cardozo, A. Thevenet and C. W. Lillehei: Comparison of Relative Merits of Occlusive and Non-Occlusive Pumps for Open Heart Surgery Together with Description of Simple Flowmetering Method for Clinical Use. J. Thoracic Surg., **36**:470, 1958.
4. Lillehei, C. W.: Discussion of Factors Influencing Survival in Total Body Perfusion. Surgery, **42**:73, 1957.
5. Lillehei, C. W. and R. A. DeWall: The Design and Clinical Application of the Helix Reservoir Pump-Oxygenator System for Extracorporeal Circulation. Postgrad. Med., **23**:561, 1958.
6. Preston, F. W., R. Nohf and O. Trippel: Neutralization of Heparin with Polybrene. Quart. Bull. N. W. Univ. Med. School, **30**:138, 1956.
7. Preston, F. W. and R. P. Parker: New Antiheparin Agent (Polybrene): Effect in Peptone Shock and in Experimental Radiation Injury. A. M. A. Arch. Surg., **66**:545, 1953.
8. Weiss, W. H., J. S. Gilman, A. J. Catevacci and A. E. Osterberg: Heparin Neutralization with Polybrene Administered Intravenously. J. A. M. A., **166**:603, 1958.