Dextran Prophylaxis in Surgery

RONALD BRISMAN,* M.D., LEON C. PARKS, M.D.,
J. ALEX HALLER, JR., M.D.

From the Department of Surgery, The Johns Hopkins Hospital, Baltimore, Maryland

PULMONARY embolism is a significant cause of morbidity and mortality in high risk surgical patients. Several studies have shown that anticoagulants (heparin or warfarin) can prevent pulmonary emboli in these patients.[3, 8, 16-19] The bleeding complications associated with anticoagulants prohibit their use in many postoperative patients. Dextran 75 (average molecular weight 75,000), another anti-thrombotic agent, has been reported to prevent postoperative pulmonary embolism without causing bleeding diathesis.[2, 22] Conflicting results were obtained in another investigation, which was unable to demonstrate benefit from the prophylactic use of dextran 75.[10] The following prospective, double-blinded, randomly allocated controlled study tries to determine the effectiveness of dextran 75 in preventing pulmonary emboli in high risk surgical patients.

Method

Surgical patients who had a high risk for developing pulmonary embolism were selected (Table 1). Written permission was obtained from each patient after the purpose and risks of the study were explained. Not all patients who fit into the specified categories were included in the study due to individual physician or patient refusal. Patients were assigned according to a random table to receive a coded solution of either dextran 75 (6% solution) in dextrose 5% water or plain dextrose 5% water. The code was established by the hospital pharmacy and was not broken until the termination of the study, including evaluation of the data.

Coded solutions were administered as an initial 500 ml. intravenous infusion during a 3- to 5-hour period. The first infusion was begun by a physician at least 5 minutes prior to induction of anesthesia. Subsequent daily infusions were given at a dose of 5 ml./Kg. body weight until 24 hours after a patient began active ambulation. Early ambulation was encouraged in each patient.

Each patient was evaluated daily for signs and symptoms of pulmonary embolism and thrombophlebitis by the resident staff and investigators. Patients were classified as "suspect" for pulmonary embolism when suggestive symptoms or signs developed (Table 2). Each "suspect" patient had serial determinations of lactic dehydrogenase (LDH), serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), bilirubin, chest x-ray, electrocardiograms and lung scan.

The clinical diagnosis of pulmonary embolism was based on clinical impression and, in each case, the presence of both a positive lung scan and a "typical" enzyme pattern. Lung scans were considered posi-

Submitted for publication July 29, 1970.

Supported in part by U.S.P.H.S. Gen. Res. Support Grant No. 5 S01 SR 5378.

Reprint requests to Dr. Leon C. Parks, 550 N. Broadway, Baltimore, Maryland 21205.

* Department of Neurological Surgery, Neurological Institute, New York.

TABLE 1. *Selection of Patients for Study*

Patients aged 60 or more years undergoing operations expected to necessitate more than 3 days' bed rest
Patients aged 30 or more years with obesity, visceral malignant disease, major burns, peritonitis, or surgical dissection within the pelvis or lower extremity
The presence of severe cardiopulmonary disease
A history of thromboembolic disease

tive when perfusion defects were found in the presence of a normal chest x-ray. A "typical" enzyme pattern consisted of an abnormal and sequentially elevated LDH in the presence of a normal and unchanging SGOT.[21] A diagnosis of thrombophlebitis was made if calf tenderness, swelling and Homan's sign were present.

A preliminary analysis was prepared to estimate the number of patients necessary to obtain statistically significant data. On the basis of a pilot study on 53 patients and a review of the literature,[19] it was anticipated that an incidence of pulmonary emboli in the high risk surgical control patients would approach 10%. An arbitrarily selected incidence of 3% (or fewer) pulmonary emboli in the dextran treated group would be regarded as significant prophylaxis. A sample size of 200 patients in each group (dextran and control) would be necessary to detect such a difference with a probability of claiming treatment effective when no difference existed of 0.05 and probability of failure to achieve statistical significance of 0.10.

TABLE 2. *Basis for Designation of Patients as "Suspect" for Pulmonary Embolism*

De novo cardiopulmonary symptoms and signs (chest pain, dyspnea, cough, tachycardia, wheezing)
Fever with no obvious cause
Sudden onset of upper abdominal pain
Unexplained shock
Thrombophlebitis
Unexplained anxiety with failure to improve as expected

Results

One hundred seventy-nine high risk surgical patients were studied between January and May 1967. Eighty-nine received dextran 75 and 90 received plain dextrose 5% water. Both groups were comparable as to age, sex, race and surgical procedure (Table 3).

In the control group (dextrose 5 per cent water), six (6.7%) developed pulmonary embolism and nine (10%) clinical thrombophlebitis (Table 4). Thrombophlebitis and pulmonary embolism occurred concurrently in only one patient. Pulmonary embolism was diagnosed clinically in five patients. Two were examined at autopsy and gross pulmonary emboli were found. Pulmonary embolism was not diagnosed clinically in one patient who had microscopic emboli at autopsy.

In the dextran group, eight (9.0%) developed pulmonary embolism and three had thrombophlebitis (3.4%). Pulmonary embolism was diagnosed clinically in seven patients. In three gross pulmonary emboli were found at autopsy. Pulmonary embolism was not diagnosed clinically in one patient in whom microscopic emboli were found at autopsy.

Five died and three underwent autopsy in the control group and there were eight deaths with six autopsies in the dextran group. Pulmonary embolism was not thought to be the immediate cause of death in any of the patients. None of the six without gross pulmonary emboli at autopsy had been diagnosed clinically as having emboli. One had been an "embolus suspect" for what proved to be bronchopneumonia.

Dextran did not apparently contribute to any of the deaths. None of the patients receiving dextran developed bleeding diathesis. The only complications of dextran were severe anaphylactoid reactions which occurred within 30 seconds of initial infusion in three patients.[5] These were characterized

TABLE 3. *Characteristics of the Patient Population (the numbers in parenthesis refer to clinically significant pulmonary emboli in each group)*

Characteristic	Control Group (No. of Patients)	Dextran Group (No. of Patients)
Totals	90 (5)	89 (7)
Age:		
less than 30 yr.	4	4
30–39 yr.	8	4
40–49 yr.	15	8
50–59 yr.	17 (1)	16 (2)
60–69 yr.	8 (1)	23 (2)
70–79 yr.	27 (2)	28 (3)
80 plus yr.	11 (1)	8
	Avg. age 62	Avg. age 63
Sex:		
Male	61 (3)	57 (5)
Female	29 (2)	32 (2)
Race:		
Negro	63 (4)	66 (5)
White	27 (1)	23 (2)
Economics:		
Ward	64 (4)	68 (6)
Private	26 (1)	21 (1)
Surgical procedure:		
Severe burn	—	1
Radical neck dissection	2	1
Radical mastectomy	2	5
Thoracotomy for pulmonary resection	4	7
Surgical procedure:		
Hiatal herniorrhaphy	1	2
Subtotal gastric resection	1	3 (1)
Vagotomy and pyloroplasty	4	1
Lysis small bowel adhesions	1 (1)	1
Subtotal colectomy	4	8 (1)
Abdominal-perineal resection	5	4 (1)
Cholecystectomy	12	9 (1)
Cholecysto-jejunostomy, pancreatic cancer	4 (1)	1
Whipple resection	—	1
Abdominal aneurysectomy	3	1
Aorto-iliac or Fem. popliteal bypass	5	2
Inguinal herniorrhaphy	5	6 (1)
Radical inguinal node dissection	—	1
Lumbar sympathectomy	1	1
Nephrectomy	4	2
Subtotal cystectomy	1	3
Transuretheral prostatectomy	13 (1)	10 (2)
Retropubic prostatectomy	7 (1)	9
Above-knee amputation	5	4
Below-knee amputation	3 (1)	4
Varicose vein ligation and stripping	1	3

by severe apprehension, nausea, vomiting, defecation and hypotension. All patients were successfully resuscitated.

Discussion

Dextran can prevent some experimental arterial [5] and venous [12] thrombosis. The antithrombotic effect of dextran depends on its mean molecular weight and is most effective when dextran 75 (mean molecular weight 75,000) is used.[5] The antithrombotic action of dextran may be related to its ability to decrease platelet adhesiveness [22] and interfere with platelet aggregation.[6]

Several studies used dextran prophylactically to prevent postoperative pulmonary emboli,[2, 10, 13, 22] but the data are equivocal. The present prospective and controlled study was designed to show whether or not dextran was able to prevent pulmonary emboli in high risk surgical patients. Although a larger series of patients was initially anticipated, the study was terminated after 179 patients had been evaluated for three reasons. First, the incidence of pulmonary emboli was even higher (9.0%) in the dextran treated group than in the controls (6.7%). Second, the mortality in the dex-

TABLE 4. *Thromboembolic Disease and Mortality in Control and Dextran-Treated Patients*

	Control	Dextran	Total
Pulmonary embolization	6	8	14
Clinical diagnosis only	3	4	7
Autopsy diagnosis			
Gross	*2	*3	*5
Microscopic	1		2
Thrombophlebitis	9	3	12
Thrombophlebitis and pul. emb.	1	0	1
Total deaths	5	8	13
Patients autopsied	3	6	9

* Clinical and autopsy diagnoses.

tran treated group (9.0%) was higher than in the controls (5.6%). Third, the last two patients to enter the study sustained severe immediate anaphylactoid reactions to the dextran. This brought the total of such reactions to three of 89 patients receiving dextran. Each reaction was associated with definite but transient morbidity, the last of which was almost fatal. It became apparent that any possible beneficial prophylactic effect of the dextran was obviated by the known severe iatrogenic anaphylactoid complications.

The effectiveness of dextran 75 in treating thrombophlebitis has been demonstrated.[7] The ability of dextran to prevent thrombophlebitis in high risk surgical patients has also been suggested,[1, 11, 13, 20] although one report failed to show this effect.[10] The present study suggests that dextran 75 may prevent thrombophlebitis in some patients. The incidence of thrombophlebitis in the patients receiving dextran (3.4%) was less than in the control group (10%). This may reflect the ability of dextran to prevent the "platelet thrombus" which forms in the presence of intimal damage.

Why does dextran prevent thrombophlebitis but fail to prevent pulmonary emboli? Although dextran can preven the "platelet thrombus" it is unable in similar doses (0.9 Gm./Kg. body weight) to prevent the "coagulation thrombus" resulting from stasis and hypercoagulability.[9] The latter may be an additional source for pulmonary embolization.

Summary

A prospective, double-blind, randomly allocated study on 179 patients has been performed in an effort to determine the effectiveness of dextran 75 in preventing pulmonary emboli in high risk surgical patients. Coded solutions of dextran 75 or dextrose 5% water were infused before operation as an initial intravenous infusion of 500 ml. during a 3 to 5 hour period, with subsequent daily infusions of 5 ml./Kg. until active ambulation had begun. The incidence of pulmonary emboli, 9.0% (eight of 89) in the dextran group and 6.7% (six of 90) in the controls, was not reduced by dextran. The over-all mortality, 9.0% (eight of 89) in the dextran group and 5.6% (five of 90) in the controls, was not decreased by dextran. Thrombophlebitis occurred less often in the dextran group 3.4% (three of 89) than in the controls, 10% (nine of 90). Three cases of anaphylactoid reaction occurred in the dextran group. Dextran 75 is not recommended for prophylaxis of pulmonary emboli in high risk surgical patients. It may be of value, in selected cases, for preventing thrombophlebitis.

References

1. Ahlberg, A., Nylander, G., Robertson, B., Cronberg, S. and Nilsson, I. M.: Dextran in Prophylaxis of Thrombosis in Fractures of the Hip. Acta Chir. Scan. Supp., **387**:83, 1967.
2. Atik, M.: The Uses of Dextran in Surgery: A Current Evaluation. Surgery, **65**:548, 1969.
3. Belding, H. H.: Use of Anticoagulants in Preventions of Venous Thromboembolic Disease in Postoperative Patients. Arch. Surg., **90**:655, 1965.
4. Brisman, R., Parks, L. C. and Haller, J. A., Jr.: Anaphylactoid Reactions Associated with the Clinical Use of Dextran 70. JAMA, **204**:824, 1968.

5. Bryant, M. F., Bloom, W. L. and Brewer, S. S.: Experimental Study of Antithrombotic Properties of Dextrans of Low Molecular Weight. Amer. Surg., **29**:256, 1963.
6. Bygdeman, S.: Prevention and Therapy of Thromboembolic Complications with Dextran. Progr. Surg., **7**:114, 1969.
7. Cox, E. F., Flotte, C. T. and Buxton, R. W.: Dextran in the Treatment of Thrombophlebitis. Surgery, **57**:225, 1965.
8. Fagan, D. G.: Prevention of Thromboembolic Phenomena Following Operation on Neck of Femur. Lancet, **1**:846, 1964.
9. Gurewich, V. and Thomas, D. P.: Pathogenesis of Venous Thrombosis in Relation to its Prevention by Dextran and Heparin. J. Lab. Clin. Med., **66**:604, 1965.
10. Hartshorn, J. W. S., Teale, S. N. and Fair, M.: Dextran 75 and Postoperative Phlebitis, Evaluation of Dextran 75 in the Prophylaxis of Postoperative Thrombophlebitis, Pulmonary Embolism, and Myocardial Infarction. Arch. Surg., **98**:694, 1969.
11. Jansen, H.: Dextran as a Prophylaxis Against Thromboembolism in General Surgery. Acta Chir. Scan. Supp., **387**:86, 1967.
12. Just-Viera, J. O. and Yeager, G. H.: Protection From Thrombosis in Large Veins. Surg. Gynec. Obstet., **118**:354, 1964.
13. Koekenberg, L. J. L.: Experimental Use of Macrodex as a Prophylaxis Against Post-Operative Thromboembolism. Bull. Soc. Int. Chir., **21**:501, 1962.
14. Langdell, R. D., Adelson, E., Furth, F. W. and Crosby, W. H.: Dextran and Prolonged Bleeding Time. JAMA, **166**:346, 1958.
15. Nilsson, I. M. and Eiken, O.: Further Studies on the Effect of Dextran of Various Molecular Weight on the Coagulation Mechanism. Thromb. Diath. Haemorrh., **11**:39, 1964.
16. Salzman, E. W., Harris, W. H. and DeSanctis, R. W.: Anticoagulation for Prevention of Thromboembolism Following Fractures of the Hip. New Eng. J. Med., **275**:122, 1966.
17. Sharnoff, J. G.: Results in the Prophylaxis of Postoperative Thromboembolism. Surg. Gynec. Obstet., **123**:303, 1966.
18. Sevitt, S. and Gallagher, N. G.: Prevention of Venous Thrombosis and Pulmonary Embolism in Injured Patients. Lancet, **2**:981, 1959.
19. Skinner, D. B. and Salzman, E. W.: Anticoagulant Prophylaxis in Surgical Patients. Surg. Gynec. Obstet., **125**:741, 1961.
20. Stadil, F.: Macrodex Prophylaxis in Postoperative Thrombosis. A Preliminary Communication. Acta Chir. Scan. Supp., **387**:88, 1967.
21. Wacker, W. E. and Snodgrass, P. J.: Serum LDH Activity in Pulmonary Embolism Diagnosis. JAMA, **174**:2142, 1960.
22. Wichman, H., Atik, M. and Harkness, J. W.: The Use of Dextran in the Prevention of Thromboembolism in Patients with Major Fractures. Surg. Forum, **19**:467, 1968.