

Prophylactic efficacy of low-dose dihydroergotamine and heparin in postoperative deep venous thrombosis following intra-abdominal operations

Multicenter Trial Committee, Philadelphia, Pa.

Postoperative pulmonary embolism continues to be a problem in patient care, especially in high-risk patients. This study was designed to evaluate a combined pharmacologic approach to the prophylaxis of postoperative deep venous thrombosis (DVT) by mediating at least two and probably three of Virchow's predisposing factors. Patients 40 years of age and older undergoing operations greater than 45 minutes under general anesthesia were placed in one of five treatment groups and studied by a prospective randomized, double-blind protocol. Study drugs were the following: (1) 0.5 mg of dihydroergotamine plus 5000 IU of sodium heparin (DHE 5000), (2) 0.5 mg DHE plus 2500 IU heparin (DHE 2500), (3) 5000 IU of HEP (HEP 5000), (4) 0.5 mg of DHE (DHE 0.5), and (5) a placebo. Study medications were administered 2 hours preoperatively and continuously thereafter every 12 hours postoperatively subcutaneously in the anterior abdominal wall for 5 to 7 days or until a positive radiofibrinogen uptake test (RFUT). The RFUT was performed according to standardized technique and was used to establish the presence or absence of DVT. This report is an analysis of the major subgroup of patients undergoing intra-abdominal operations. Results showed a highly statistically significant prophylactic benefit from DHE 5000 compared with the placebo ($p < 0.003$) and all other treatment groups ($p < 0.05$). There was no significant benefit from DHE 2500, HEP 5000 ($p > 0.13$), and DHE 0.5 ($p > 0.3$). All patients who entered the study had two or more risk factors for postoperative DVT, and high-risk patients were distributed equally throughout all treatment groups. DHE 5000 maintained its prophylactic benefit in high-risk patients. Evaluation of operative blood loss, postoperative blood loss, hematomas (wound or injection site), hematuria, postoperative hemoglobin difference, and adverse reactions revealed no significant difference between the study medications and the placebo. It is proposed that DHE 5000 has a synergistic prophylactic effect by mediating all three limbs of Virchow's triad: hypercoagulability (heparin), stasis (DHE), and vein wall injury secondary to venodilatation (DHE). DHE 5000 is recommended for patients at high risk of developing postoperative DVT and pulmonary embolism; however, it should be avoided in patients with acute myocardial infarction, sepsis, and sustained hypotension. (*J VASC SURG* 1984; 1:608-16.)

Pulmonary embolism continues to be a major complication in patients following intra-abdominal operations. Although it is difficult to precisely determine the true incidence of fatal pulmonary embolism, the best available data reveal an incidence of 0.2% to 0.5%.¹⁻³ The morbidity of nonfatal pulmonary emboli is significant, and anticoagulation therapy in the immediate postoperative period fol-

lowed by long-term anticoagulation therapy imposes added risk. It is commonly accepted that the major deep veins (femoral and iliac) are the primary source of pulmonary emboli. Unfortunately, the signs and symptoms of deep venous thrombosis (DVT) are obscure,⁴ and the diagnosis is elusive prior to the embolic event.⁵ If DVT can be minimized or eliminated, it is reasonable that the frequency of pulmonary embolism will likewise be reduced.

The site of origin of DVT is an area of controversy, with some investigators suggesting that thrombi begin independently in the iliofemoral

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segment⁶ and others maintaining that the origin is most frequently in the calf veins.⁷ If postoperative patients are to be monitored for the development of DVT and if the monitoring technique is sensitive for calf vein thrombosis, then it is important that calf vein thrombosis be a dominant marker for developing clots in the deep venous system. Whether the thrombus originates in the calf veins and extends into the more proximal veins or the two segments develop thrombosis simultaneously but independently is less important. Available data suggest that there is a close association of calf vein thrombosis and major proximal vein thrombosis in general surgical patients.⁷⁻⁹ Isolated proximal vein thrombosis is more common in orthopedic patients, whereas it is unusual in general surgical patients.⁸

In 1856 Virchow¹⁰ presented the classic triad of the factors leading to DVT. Included are stasis, the hypercoagulable state, and vein wall injury. As one attempts to establish the pathophysiology of DVT, it becomes apparent that all three elements play a role. A single component of the triad may be the overwhelming disorder in a particular instance, but for most the pathogenesis is multifactorial.

Numerous methods of DVT prophylaxis have been investigated. Mechanical methods are aimed at diminishing "stasis" and increasing venous return. Plasma expanders likewise are directed toward minimizing stasis; however, effects on platelet kinetics and coagulation factors have been demonstrated. Anticoagulants and particularly low-dose heparin have been studied in many clinical trials; and while conflicting data exist, heparin has generally been

shown to be effective in reducing the frequency of postoperative DVT in general surgical patients.¹¹⁻¹³

There has not been uniform acceptance by U.S. surgeons of any prophylactic regimen. There are many reasons for the lack of uniform acceptance. Included are thoughts that the incidence of DVT in the United States may not be as high as demonstrated in other countries¹⁴; the potential hemorrhagic complications from the administration of low-dose heparin; the question of how the positive radiofibrinogen uptake test (RFUT) relates to the risk of pulmonary embolism and postthrombotic symptoms; and the lack of well-controlled studies performed in this country.¹¹

If one were to postulate a new method for the prophylaxis of DVT, an approach directed at inhibiting at least two of Virchow's three factors would seem advantageous. Low-dose dihydroergotamine (DHE) has been shown to exert a selective constrictive effect on veins and venules (capacitance vessels) without affecting arteries and arterioles (resistance vessels).^{15,16} This effect counteracts venous stasis and accelerates venous return. Several European clinical trials demonstrated significant prophylactic efficacy with low-dose DHE.¹⁷

Because of the available data, it was thought that a well-controlled study of the relative efficacy of treatment regimens involving DHE and/or heparin was indicated. A large prospective multicenter trial was performed in the United States (Table I). This report is an analysis of the major subgroup of patients undergoing intra-abdominal operations. The general surgeon is most often faced with the patient

Table II. Exclusion criteria

Myocardial infarction <6 mo
Angina at rest
Anticoagulants
Platelet inhibitors
Plasma expanders (dextran type)
Postphlebotic limb
Varicose veins
Severe peripheral vascular disease
Uncontrolled hypertension
History of bleeding disorder
Hypersensitivity to:
Ergot derivatives
Heparin
Lidocaine
Iodine
Pregnancy

Table III. Protocol violations

Category	No.
Improperly administered study medication	19
Unallowed concomitant medication	19
¹²⁵ I-fibrinogen not given	13
Adverse reaction	12
Uncooperative patient	11
Early hospital discharge	10
Non-drug-related cause	9
Excessive bleeding	9
RFUTs not performed	9
Administrative problem	7
Patient died	6
Patient discontinued	5
Concomitant radioisotope	5
Operation cancelled	4
Non-general anesthesia	3
Personal reasons	2
Under age	1
	<u>144</u>

at high risk for postoperative pulmonary embolism. Because laparotomy is the major procedure of the general surgeon, it is important to establish the risks vs. benefits of any prophylactic DVT regimen in this important patient population.

METHODS

Fifteen medical centers participated in this investigation, which was organized as a prospective double-blind, parallel group clinical trial. Institutional review board approval of the protocol and informed consent statements were obtained from each center.

Patients entering this study were required to be at least 40 years of age, scheduled for a major operation exceeding 45 minutes, and requiring general anesthesia and a minimum 5-day postoperative period of hospitalization. A normal preoperative coagulation profile, which included platelet count, bleeding time,

Table IV. Risk factors*

Previous pulmonary embolism
Previous DVT
Malignancy
Varicose veins
Previous myocardial infarction
Angina pectoris
Previous long bone fracture
Chronic obstructive pulmonary disease
Contraceptives

*No difference among treatment groups.

prothrombin time, and partial thromboplastin time, was required.

Only patients undergoing major intra-abdominal operations are included in this analysis. Thoracotomy, mastectomy, inguinal herniorrhaphy, prostatectomy, and lower genitourinary tract operations were eliminated. Additional patient exclusion criteria are listed in Table II.

After informed consent was obtained, each patient was randomly assigned to one of five treatment groups.

1. DHE 5000: a combination of 0.5 mg of dihydroergotamine and 5000 IU of heparin sodium
2. DHE 2500: 0.5 mg of dihydroergotamine plus 2500 IU of heparin sodium
3. HEP 5000: 5000 IU of heparin sodium
4. DHE 0.5: 0.5 mg of dihydroergotamine
5. Placebo

The study medications were administered by subcutaneous injection into the anterior abdominal wall beginning 2 hours prior to operation and continuing thereafter every 12 hours for a minimum of 5 days or the development of a positive RFUT.

The criterion for diagnosis of DVT was the RFUT. This test measures the incorporation of ¹²⁵I-fibrinogen into actively forming thrombi or previously established thrombi that continue to enlarge.¹⁸ One hundred milligrams of potassium iodide was given orally to each patient the evening before operation and daily thereafter (whenever possible) for 5 days to act as a thyroid-blocking agent. Each patient received 100 μ Ci of ¹²⁵I-fibrinogen intravenously during the immediate postoperative period. RFUT measurements were begun 4 hours after the administration of ¹²⁵I-fibrinogen and performed daily until the patient had completed the 5- to 7-day treatment course. A portable isotope localization monitor (Ibrinator) was used to measure the ¹²⁵I-fibrinogen over four distinct points on the medial aspect of the middle to lower thigh and six distinct points on the posterior aspect of the

Table V. Risk factor distribution per treatment group*

No. of risk factors	DHE 5000	DHE 2500	HEP 5000	DHE 0.5	Placebo	Total
2	36 (24%)	44 (27%)	38 (24%)	15 (21%)	27 (34%)	160 (26%)
3	63 (41%)	70 (43%)	69 (44%)	33 (45%)	28 (35%)	263 (42%)
4	43 (28%)	37 (23%)	34 (22%)	21 (29%)	15 (19%)	150 (24%)
≥5	11 (7%)	13 (8%)	15 (10%)	4 (5%)	9 (11%)	52 (8%)
	<u>153</u>	<u>164</u>	<u>156</u>	<u>73</u>	<u>79</u>	<u>625</u>

Chi square (12 *df*) = 9.891; Prob > chi = 0.6255.

Table VI. Comparative DVT incidence rates

Treatment	Total No.	Counts		Pairwise comparisons (exact <i>p</i> level)*			
		DVT	No DVT	2	3	4	5
1. DHE 5000	153	14 (9.2)	139 (90.8)	0.0271	0.0253	0.0295	0.0024
2. DHE 2500	164	28 (17.1)	136 (82.9)		1.000	0.4122	0.1326
3. HEP 5000	156	27 (17.3)	129 (82.7)			0.8534	0.1455
4. DHE 0.5	73	14 (19.2)	59 (80.8)				0.2983
5. Placebo	79	19 (24.1)	60 (75.9)				

Numbers in parentheses are percentages.

*Based on Fisher's exact test. Comparisons among DHE 2500, HEP 5000, and DHE 0.5 are two tailed. All other comparisons are two tailed.

popliteal fossa (2 points) and calf (4 points). The diagnosis of DVT was established if there was at least a 20% difference in radiofibrinogen uptake that persisted for 24 hours and was detected at any anatomic point compared with the readings over adjacent points of the same leg or the same anatomic point compared with previous readings and the corresponding point on the opposite leg.

The variables that were analyzed to monitor the safety of the drug medication included the following: (1) operative blood loss, (2) postoperative blood loss, (3) excessive postoperative bleeding (a subjective judgment of the attending physician), (4) hematoma formation either at the wound or the injection site (daily evaluation), (5) hematuria (micro- or macroscopic), (6) pre- and postoperative hemoglobin determinations, and (7) adverse drug reactions.

RESULTS

Seven hundred sixty-nine patients having intra-abdominal operations were selected for this analysis, which is part of a larger study being reported elsewhere. Six hundred twenty-five (81%) patients completed the study according to protocol requirements. Reasons for protocol violation are listed in

Table III. Comparison of the distribution of protocol compliers and violators showed no difference between treatment groups.

The average age of patients completing this study was 60.2 years. Fifty-one percent of the patients were between 40 and 60 years of age, and 49% were older than 60 years of age. There was a relatively equal sex distribution (55% men and 45% women). The anthropomorphic characteristics of patients showed that 61% had medium frames, 22% small frames, and 17% large frames. Obesity was defined as greater than 15% above ideal body weight; 35% (220) of patients were considered to be in this category. The average weight of the men was 170.5 pounds, and the average weight of the women was 157.1 pounds.

Existing risk factors for each patient were identified according to those listed in Table IV. The risk factors were distributed equally throughout all treatment groups (Table V); therefore, the patients in each study group were at similar risk for DVT. All patients entered had at least two risk factors; 74% had three or more.

The incidence rates of thrombosis for each of the treatment groups is illustrated by the bar graph in Fig. 1. The DVT incidence observed for each of the

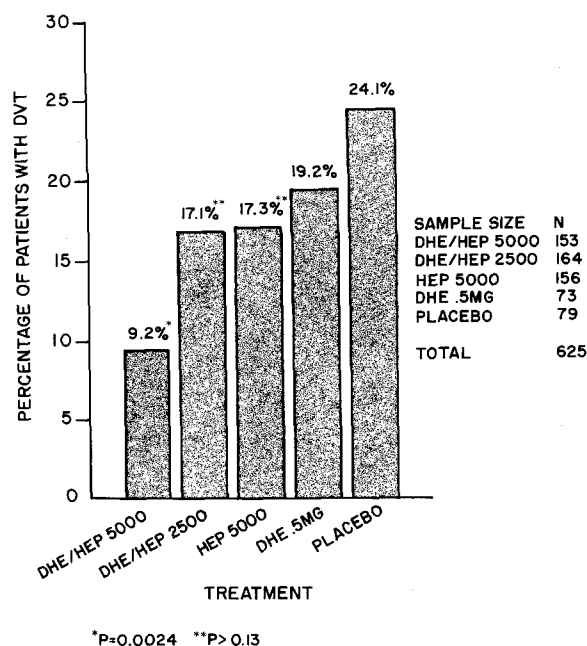


Fig. 1. DVT incidence rates by treatment group. There was a trend in reduction in postoperative DVT for all treatment groups. Statistical significance was achieved by only DHE 5000 ($p < 0.003$), whereas DHE 2500 and HEP 5000 achieved a significance of $p > 0.13$. Number of patients successfully completing protocol in each treatment group is listed at right of bar graph.

five treatment groups was placebo, 24.1%; DHE 0.5, 19.2%; HEP 5000, 17.3%; DHE 2500, 17.1%; and DHE 5000, 9.2%. A reduction in the incidence of DVT was demonstrated in each treatment group. Compared with the placebo, DHE 0.5 showed a 20% reduction in DVT, HEP 5000 a 28% reduction, DHE 2500 a 29% reduction, and DHE 5000 a 62% reduction. The number of patients completing this study in each treatment group, the incidence of DVT, and the intergroup statistical comparisons of DVT incidence rates are shown in Table VI.

The pairwise comparison of treatment groups showed that DHE 5000 was significantly superior to the placebo ($p < 0.003$) and to all other treatment groups (vs. DHE 2500, HEP 5000, and DHE 0.5 $p < 0.03$). Although DHE 2500 and HEP 5000 appeared to be similarly effective in reducing the incidence of DVT, the effect was not statistically significant compared with the placebo ($p < 0.14$ and $p < 0.15$, respectively). The patients treated with DHE 0.5 had a marginal reduction in the incidence of DVT, which likewise was not significant ($p < 0.3$).

Operative and postoperative hemorrhagic events were major considerations in the safety analysis of

the study drugs. Table VII is a detailed compilation of all aspects of blood loss monitored during the study. Characterization of blood loss included measured intraoperative loss, patients losing more than vs. less than 1 unit of blood, postoperative drainage, subjective impression of "excessive postoperative bleeding," documentation of blood replacement, and hematoma formation either at the operative wound or the injection site of the study medication. The overall analysis reveals no statistically significant difference among treatment groups for any of these measurements. The mean postoperative drainage shows a trend for higher values measured in the DHE 5000 and DHE 2500 groups, but on closer examination this difference was attributed to a few outliers in these two groups. Of the few patients in this category, the attending physician thought that only one had "excessive" postoperative bleeding. Because the few extremely large outlying values tend to skew the means, the median values that are similar across groups are more meaningful estimates of central tendency. All cases included, the differences in means are not statistically significant.

It is interesting to note that there was no significant difference in the incidence of wound or injection site hematoma. One serious complication occurred in a patient who received DHE 5000, and it may have contributed to his death. Although the cause of death was disseminated intravascular coagulation and sepsis attributable to bowel necrosis, the potentiating effect of DHE on vasoconstriction in sepsis and hypotensive patients must be considered.

DISCUSSION

The results of this trial show a significant prophylactic benefit from postoperative DVT when the combination of DHE 0.5 and HEP 5000 was injected subcutaneously 2 hours preoperatively and every 12 hours postoperatively. In view of the numerous studies in the literature that substantiate significant prophylaxis with low-dose heparin alone, it was surprising to note that HEP 5000 or the combination of DHE 2500 did not show significant prophylactic benefit in this series.

There were no additional complications in the treatment groups when compared with the placebo. Specifically, there was no difference between treatment groups in any of the blood loss parameters. Patients who have significant myocardial ischemia, sepsis, or hypotension should not be treated with DHE.¹⁹ It is also suggested that patients currently being treated with the DHE-heparin combination who develop any conditions initially considered ex-

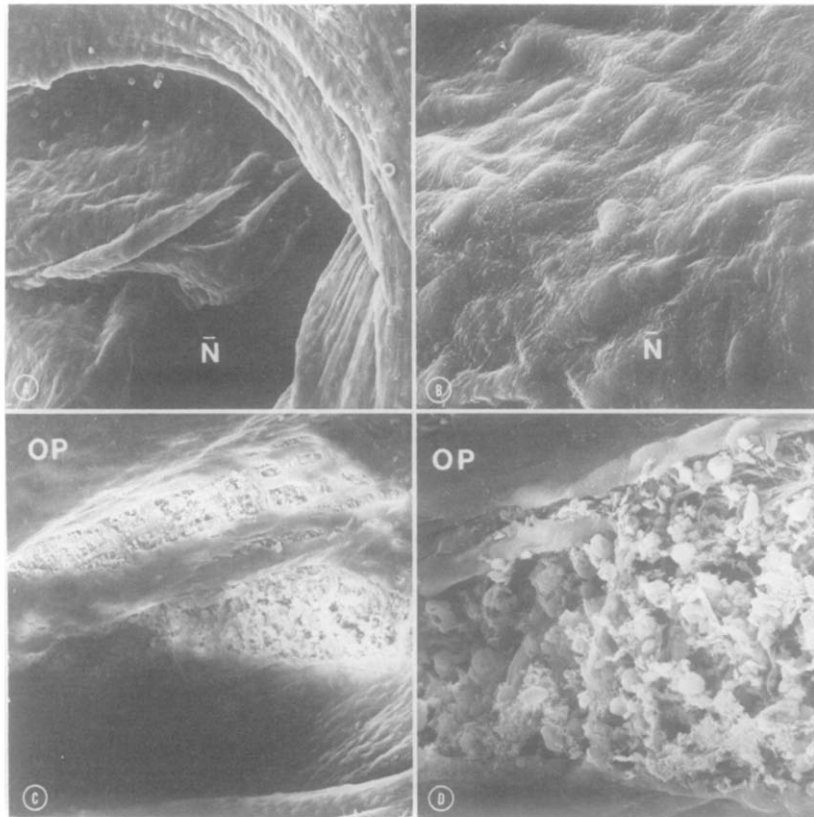


Fig. 2. A, Jugular venous confluence of anesthetized but nonoperated dog showing normal endothelium with complete integrity and no thrombus formation. B, Higher magnification of same vein segment. C, Jugular venous confluence of operated dog showing laceration extending through endothelium and basement membrane. This injury represents inability of venous endothelium to accommodate to significant smooth muscle response (venodilation) of operative trauma. D, Higher magnification of venous laceration showing thrombus formation (WBCs, RBCs, platelets, and fibrin).

clusion criteria be discontinued from their medication.

Clearly not all patients undergoing general surgical procedures need be treated with venous thrombosis prophylaxis. However, patients in high-risk groups stand to benefit significantly, and it has been shown that DHE 5000 maintains its prophylactic efficacy in patients with multiple risk factors.

Patients undergoing abdominal operations are at highest risk of developing DVT within the first 4 postoperative days.^{7,20} This suggests that the trauma of operation creates an environment responsible for the formation of thrombi. The supine position, immobility, and venodilatation are thought to be factors that contribute to stasis. The prolonged retention of dye in the soleal sinuses has been demonstrated in immobile patients,^{21,22} and investigators have shown a reduction in venous flow velocity.²³ Hypercoagulability is thought to occur to some degree with operation,^{24,25} although it may be difficult

to define. Vein wall injury is a common precursor to DVT following direct trauma; however, recently it has been shown that there is a reproducible injury in remote veins following operations.²⁶

It was found that when DHE was combined with heparin, there was an added prophylactic benefit compared with heparin alone.^{27,28} The mechanism proposed to explain these results is the apparent increased venous tone with improvement of venous return and accelerated venous flow velocity. Kakkar et al.²⁸ showed that patients receiving the combination of DHE and heparin sustained a significantly higher heparin level than those receiving heparin alone. However, Schran et al.²⁹ failed to reproduce that finding in a more recent study that investigated the pharmacokinetics and bioavailability of this combination.

The mechanism of action of the DHE-heparin combination appears to be synergistic since all three limbs of Virchow's triad are potentially affected. In

Table VII. Safety analysis of study drugs

Blood loss category	DHE 5000	DHE 2500	HEP 5000	DHE 0.5	Placebo	Total
Intraoperative (ml)						
Mean	533	481	486	542	690	529
Median	300	300	300	300	400	300
No. \geq 500 ml	50 (34%)	46 (29%)	50 (35%)	28 (39%)	32 (43%)	206 (35%)
No. < 500 ml	97 (66%)	111 (71%)	94 (65%)	44 (61%)	43 (57%)	389 (65%)
Postoperative drainage (ml)						
Mean	188	146	90	73	117	131
Median	50	50	50	50	68	50
Excessive postoperative bleeding	1 (1%)	5 (3%)	2 (1%)	0 (0%)	1 (1%)	9 (1%)
Total blood replaced (ml)						
Mean	396	330	347	396	412	369
Median	0	0	0	0	0	0
Hematoma						
Wound	5 (3%)	3 (2%)	4 (3%)	1 (1%)	1 (1%)	14 (2%)
Injection site	18 (12%)	21 (13%)	20 (13%)	6 (8%)	6 (8%)	71 (11%)
Postoperative hemoglobin drop (mean)						
Day 3	-1.23	-1.21	-1.18	-1.10	-1.57	
Day 5	-1.21	-1.29	-1.03	-0.93	-1.27	
Hematuria (% of patients not catheterized)						
Day 3	34	21	15	28	23	
Day 5	18	26	18	10	14	

the canine model Stewart et al.²⁶ have shown venous intimal lacerations in areas of venous confluences following total hip replacement. They likewise have demonstrated distant vein wall abnormalities following abdominal surgery and found that this damage could be reproduced with the infusion of vasoactive amines.^{30,31} Subsequent studies likewise show that tears through the venous endothelium and basement membrane served as foci for thrombogenesis and were induced around venous confluences in response to surgically induced trauma or infused vasoactive amines¹ (Fig. 2). Because DHE markedly reduces venodilatation, it can be postulated that intimal lacerations that occur secondary to the pronounced response of vascular smooth muscle would be reduced. Therefore DHE can potentially decrease vein wall injury. It has been shown that DHE reduces stasis by increasing venous flow velocity. The anticoagulant heparin is directed toward minimizing the hypercoagulable state. Therefore it can be concluded that the combination of DHE and heparin affects each limb of Virchow's triad, and one would naturally expect synergistic improvement in prophylactic benefit when the two are used in combination rather than each alone.

CONCLUSIONS

1. DHE 5000 given 2 hours preoperatively and continuously thereafter every 12 hours postoperatively reduces the risk of DVT in the lower extremities following intra-abdominal operations in patients 40 years of age or older.

2. DHE 5000 is significantly superior to HEP 5000, DHE alone, or DHE 2500. DHE 5000 maintains its prophylactic benefit when administered to high-risk patients.
3. No significant side effects, adverse drug reactions, or hemorrhagic complications were found.
4. DHE should not be administered in the presence of overt sepsis or sustained hypotension.
5. The proposed mechanism for prophylactic effect is through mediating all three limbs of Virchow's triad by minimizing the hypercoagulable state (heparin), decreasing stasis by increasing venous flow velocity (DHE), and decreasing vein wall injury by limiting venodilatation (DHE).

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REFERENCES

1. Aksoy MD, Zerweck CR, Stewart GJ. Smooth muscle as a factor in the pathogenesis of deep venous thrombosis—contractility of canine jugular and femoral veins. Proceedings, Ninth International Congress on Thrombosis and Hemostasis, Stockholm, Sweden, 1983.
2. Sasahara AA, Sharma GVRK, Barsamian EM, Schoolman M, Cella G. Pulmonary embolism—Diagnosis and treatment. JAMA 1983; 29:2945-50.
3. Wessler S. Venous thromboembolism: Scope of the problem. In: Frantantoni J, Wessler S, eds. Prophylactic therapy of deep vein thrombosis and pulmonary embolism. US Dept of Health, Education and Welfare publication No. (NIH) 76-866. 1975:1-10.
4. Cranley JJ, Canos AJ, Sull WJ. The diagnosis of deep venou

- thrombosis—Fallibility of clinical symptoms and signs. *Arch Surg* 1976; 111:34-36.
5. Evans DS. The early diagnosis of thromboembolism by ultrasound. *Ann R Coll Surg Engl* 1971; 49:225-49.
 6. Mavor GE, Galloway JMD. The iliofemoral venous segment as a source of pulmonary emboli. *Lancet* 1967; 1:871-4.
 7. Kakkar VV, Howe CT, Flanc C, Clarke MB. Natural history of postoperative deep vein thrombosis. *Lancet* 1969; 2: 230-2.
 8. Hull R, Hirsh J, Sackett DL, Powers P, Turpie AGG, Walker I, McBride J. The value of adding impedance plethysmography to ¹²⁵I-fibrinogen leg scanning for the detection of deep vein thrombosis in high risk surgical patients: A comparative study between patients undergoing general surgery and hip surgery. *Thromb Res* 1979; 15:227-34.
 9. Moser KM, Lemoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med* 1981; 94:439-44.
 10. Virchow R. Neuer Fall von todlicher Emboli der Lungenarterie. *Arch Pathol Anat* 1856; 10:225-8.
 11. Blaisdell WF. Low dose heparin prophylaxis of venous thrombosis: An editorial. *Am Heart J* 1979; 97:685-6.
 12. Kakkar VV. Prevention of fatal postoperative pulmonary embolism by low doses of heparin—An international multicenter trial. *Lancet* 1975; 2:45-51.
 13. Sagar S. Heparin prophylaxis against fatal postoperative pulmonary embolism. *Br Med J* 1974; 2:153-5.
 14. Bell WR, Zuidema GD. Low dose heparin—Concern and perspectives. *Surgery* 1979; 85:469-71.
 15. Lange L, Echt M. Comparative studies on drugs which increase venous tone using nor-adrenaline, ethyl-andrianol, dihydroergotamine and horsechestnut extract. *Fortschr Med* 1972; 90:1161-4.
 16. Mellander S, Nordenfelt L. Comparative effects of dihydroergotamine and noradrenaline of resistance, exchange and capacitance functions in the peripheral circulation. *Clin Sci* 1970; 39:183-201.
 17. Butterman G. Prevention of postoperative thromboembolism using a new principle of drug treatment. *Dtsch Med Wochenschr* 1975; 100:2065-9.
 18. Becker J. The diagnosis of venous thrombosis in the legs using I-labeled fibrinogen—An experimental and clinical study. *Acta Chir Scand* 1972; 138:667-81.
 19. Brazeau P. Oxytocics, oxytocin, prostaglandins, and ergot alkaloids. In: Goodman LS, Gilman A, eds. *The pharmacological basis of therapeutics*. New York: The Macmillan Co, 1975:875.
 20. Hartsuck JM, Greenfield LJ. Postoperative thromboembolism. *Arch Surg* 1973; 107:733-9.
 21. Nicolaides AN, Kakkar VV, Renney JTG. The soleal sinuses; origin of deep vein thrombosis. *Br J Surg* 1970; 57:860.
 22. Nicolaides AN, Kakkar VV, Renney JTG. Soleal sinuses and stasis. *Br J Surg* 1971; 58:307.
 23. Rieckert H. Pharmacodynamics of dihydroergotamine. Experimental findings concerning alteration of blood flow velocity in the venous system. In: Tscherne H, Deutsch E, eds. *Postoperative thromboembolic—Prophylaxe aus aktueller Sicht*. Salzburg: Schloss, Klesheim, 1980; Stuttgart: Georg Thieme Verlag, 1981:77-82.
 24. Hirsh J, Barlow GH, Kwaan HC, Saltzman EW. Diagnosis of prethrombotic state in surgical patients. *Contemp Surg* 1980; 16:65-86.
 25. Wessler S. Factors in the initiation of deep venous thrombosis. In: Nicolaides AN, ed. *Thromboembolism*. Baltimore: University Park Press, 1975:chap 2.
 26. Stewart GJ, Stone EA, Aksoy MD, Zerweck CR. Venous lesions induced in a canine model by hip replacement surgery: A study by scanning electron and light microscopy and ultrasound. *Proceedings, Ninth International Congress on Thrombosis and Hemostasis*, Stockholm, Sweden, 1983.
 27. Cotton LT. Prevention of postoperative deep venous thrombosis. *Br Med J* 1976; 2:1193.
 28. Kakkar VV, Stamatakis JD, Bently PJ. Prophylaxis for postoperative deep venous thrombosis. Synergistic effect of heparin and dihydroergotamine. *JAMA* 1979; 241:39-42.
 29. Schran HF, Bitz DW, DiSerio FJ, Hirsh J. The pharmacokinetics and bioavailability of subcutaneously administered dihydroergotamine, heparin and the dihydroergotamine-heparin combination. *Thromb Res* (In press.)
 30. Stewart GJ, Schaub RG, Niewlarowski S. Products of tissue injury—Their induction of venous endothelial damage and blood cell adhesion in the dog. *Arch Pathol Lab Med* 1980; 104:409-13.
 31. Stewart GJ, Stern HR, Schaub RG. Endothelial alterations, deposition of blood elements and increased accumulation of ¹³¹I-albumin in canine jugular veins following abdominal surgery. *Thromb Res* 1978; 12:555-63.

DISCUSSION

Dr. Andrew Nicolaides (London, England). This is a major contribution in the field of prophylaxis of deep venous thrombosis (DVT). It is a well-designed, carefully executed study that established the superiority of the combination of dihydroergotamine and 5000 units of heparin.

Although Virchow's triad is not new, the progress made in the last 10 years had made us reappraise it and give us a better understanding of the interaction among the three parts of the triad.

We now know that one factor of Virchow's triad alone is not enough to produce thrombosis. At least two should be present at one time, and we believe that in the majority of the clinical situations all three are present.

We know that a column of blood in a vein that has

been clamped will not clot as long as activated coagulation factors are not present and the endothelium is intact.

However, in the presence of activated clotting factors or damaged endothelium, the blood will thrombose; but a high blood flow will not allow this to happen even in the presence of damaged endothelium and hypercoagulable factors.

Dr. Comerota has told us how trauma can initiate a process that will damage the endothelium distally, and here is the best example of how one factor in Virchow's triad will initiate another. The understanding of this interaction has become an essential requisite for proper and rational management of prophylaxis, and I predict that we will be seeing more combinations of prophylactic methods that attack not one limb of Virchow's triad only but sev-

eral together, and I think this will be essential if we are going to prevent DVT in the high-risk groups.

Dr. W. Kirt Nichols (Columbia, Mo.). The incidence of fatal postoperative pulmonary embolism, and by inference DVT, seems to be decreasing in our institution; nonetheless, this problem continues to vex the busy clinician. Protocols that aim to reduce the incidence even further are to be applauded.

To this end the authors have added dihydroergotamine to a standard protocol of low-dose heparin. One of the proposed mechanisms of this combination is to decrease venous stasis by producing selective vasoconstriction and thereby increasing venous flow velocity. Dr. Comerota does not mention other commonly used techniques to achieve this end—such as leg elevation, elastic stockings, early ambulation, and muscle pumps.

I would like to ask two questions. Did you control this study in some way to minimize the effects of the other techniques to improve venous return? Did you measure or quantify in any way in order to confirm the impression of an increased venous flow velocity?

Dr. Michael Hume (Boston, Mass.). I want to thank the Society for a chance to mention one or two reactions to a well-designed trial, which I regret they terminated so soon because I think the numbers are small. A multicenter trial ought to have a larger experience.

We know that the combination of dihydroergotamine with heparin is an effective agent, and I am surprised that the result of their trial is to show that heparin alone was not better than the placebo. It has been in many other series. That raises some question about the entire study.

In Europe the smaller amount of heparin (2500 units) with dihydroergotamine has been shown to be effective. The advantage of the combination was that one could get by with less heparin and consequently reduce the risk of bleeding.

It is disappointing to find that that is not confirmed and that you have to use as much heparin with the dihydroergotamine as has been previously thought to be effective (heparin alone).

I am somewhat concerned, therefore, about the result and think it would have been better to have a larger total number of cases in the multicenter trial.

Dr. Comerota (closing). Dr. Bergan, we did not monitor for clinical signs of DVT. I can say from the two centers in which I was involved that most of the patients who developed positive radiofibrinogen uptake tests did not have clinical evidence of DVT.

In terms of pulmonary embolism, although this was not a realistic end point of this study, there were two patients who developed pulmonary embolism during the treatment period. One was in the placebo group (this was documented with a pulmonary angiogram), and one was suspected to have a pulmonary embolism. He was in the DHE-HEP 2500 group and had a suspicious lung scan. Both were treated for pulmonary emboli.

Mr. Nicolaidis, I thank you for your very kind comments.

Dr. Nichols, I cannot take credit for the design of this protocol. Basically, the protocol was designed by Dr. Arthur Sasahara of Boston and Dr. Frank DiSerio from Sandoz Pharmaceuticals. No other techniques were used for accelerating venous flow velocity, and all patients who had complicating factors such as any anticoagulant or antiplatelet agent given within 3 days of entrance into this study or during this study were eliminated from the protocol. One Percodan tablet during the study would eliminate the patient from consideration.

We did not document venous flow velocity and relied on the work of previous investigators.

Dr. Hume, we too were surprised that low-dose heparin at 5000 units every 12 hours did not give us an efficacious end point. However, we could not argue with the data. I think one explanation might be that the patients admitted to this study were generally high-risk patients.

I must recognize Dr. Gwendolyn Stewart of the Thrombosis Research Center of Temple University Hospital for her meticulous research, and I thank her for sharing her results with us.

It was the concerted effort of the investigators of this multicenter trial committee that permitted the successful completion of this study, and on behalf of them I thank the Society for Vascular Surgery for the opportunity to present our results.