Prevention of Deep Vein Thrombosis in Potential Neurosurgical Patients

A Randomized Trial Comparing Graduated Compression Stockings Alone or Graduated Compression Stockings Plus Intermittent Pneumatic Compression With Control

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• In a randomized trial of neurosurgical patients, groups wearing graduated compression stockings alone (group 1) or graduated compression stockings plus intermittent pneumatic compression (IPC) (group 2) were compared with an untreated control group in the prevention of deep vein thrombosis (DVT). In both active treatment groups, the graduated compression stockings were continued for 14 days or until hospital discharge, if earlier. In group 2, IPC was continued for seven days. All patients underwent DVT surveillance with iodine 125–labeled fibrinogen leg scanning and impedance plethysmography. Venography was carried out if either test became abnormal. Deep vein thrombosis occurred in seven (8.8%) of 80 patients in group 1, in seven (9.0%) of 78 patients in group 2, and in 16 (19.8%) of 81 patients in the control group. The observed differences among these rates are statistically significant. The results of this study indicate that graduated compression stockings alone or in combination with IPC are effective methods of preventing DVT in neurosurgical patients.

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) are common causes of morbidity and mortality in neurosurgical patients. The incidence of DVT detected by iodine I 125–labeled fibrinogen leg scanning and impedance plethysmography (IPG) in neurosurgical populations has been reported to be 20% to 30%.[1-4] Fatal PE occurs in approximately 1% of neurosurgical patients.[5,6]

Several methods for preventing DVT following neurosurgery are available, but the most attractive are the physical methods, including graduated compression stockings or intermittent pneumatic compression (IPC) devices.[7] Anticoagulant prophylaxis with low-dose heparin is effective in general surgical patients,[7] but the use of anticoagulants in neurosurgical patients is problematic because of the potential for serious bleeding. Antiplatelet drugs have not been universally effective for thrombosis prophylaxis and are not widely used. In a recent study in neurosurgical patients, suloctidil, a new antiplatelet drug, was found to be ineffective in preventing DVT.[4] Intermittent pneumatic compression is an effective method of prophylaxis in both general surgical patients and neurosurgical patients.[1-3,7] Despite its demonstrated efficacy, IPC is not widely used for the prevention of DVT in neurosurgical patients, possibly because of the perception that it is inconvenient to both patients and nursing staff.

Graduated compression stockings, which are much easier to use, are also effective in the prevention of DVT in general surgical patients.[8-12] However, it is not known whether graduated compression stocking prophylaxis is effective in neurosurgical patients or whether the combination of graduated compression plus IPC prophylaxis would give additional protection against thrombosis in these patients. We have therefore performed a randomized clinical trial for the prevention of DVT in neurosurgical patients comparing graduated compression stockings alone or graduated compression stockings plus IPC with a control group receiving standard physiotherapy.

PATIENTS AND METHODS

Consecutive patients 16 years of age or older admitted to the Regional Neurosciences Centre, Hamilton, Ontario, Canada, with brain tumor, spinal cord tumor, head injury, spinal cord injury, or subarachnoid hemorrhage were eligible for entry into the study. Patients were excluded if they had a history of allergy to iodine, multiple trauma involving the legs so that IPG or leg scanning could not be performed, a mild head injury requiring only 24 hours of observation, a condition that required anticoagulant therapy, or an initial abnormal IPG.

Treatment Intervention

Prior to randomization, patients were stratified by hospital admission diagnosis: brain tumor, spinal cord tumor, head injury, spinal cord injury, or subarachnoid hemorrhage; they were then assigned, according to a prescribed randomized arrangement using sealed envelopes, to one of three treatment groups. These were as follows: (1) graduated compression stockings alone, (2) graduated compression stockings plus IPC, or (3) an untreated control group. All patients received standard nursing care, including range of motion exercises.

Graduated compression stockings were supplied as T.E.D. antiembolism stockings (Kendall Company, Barrington, Ill). The stockings were supplied in nine sizes and the best fit was determined according to the patient's measurements and the manufacturer's specifications. In patients randomized to graduated compression stockings alone, the stockings were applied at the time of hospital admission. In the non–operated-on patients, the stockings were continued for 14 days or until the patient was discharged from the hospital, if earlier. In the operated-on patients, the stockings were continued for 14 days postoperatively or until the patient was discharged from the hospital, if earlier.

Intermittent pneumatic compression was applied using the T.E.D. sequential compression device (Kendall Company, Barrington, Ill), which consists of a controller and leg sleeves, divided into six chambers, attached via a plastic air hose. Compression was applied sequentially from the ankle to the thigh commencing with the two ankle chambers that inflated to a peak pressure of 45 to 50 mm Hg, followed 2½ s later by inflation of the two calf chambers to a peak pressure lower than the ankle. This was followed 3 s later by inflation of the two thigh chambers to a peak pressure lower than the calf. All six chambers remained inflated

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for an additional 5½ s after which they deflated spontaneously. During the following 60 s, the sleeves could be cooled by forced air, if desired. The inflation/deflation cycle was repeated every 71 s. Patients randomized to receive graduated compression stockings plus IPC had the graduated compression stockings applied at the time of hospital admission. In the operated-on patients, the IPC was commenced in the operating room, and in the non–operated-on patients, IPC was started within 24 hours of hospital admission. The intermittent compression was continued for seven days and the graduated compression stockings continued for 14 days or until the patient was discharged from the hospital, if earlier. All patients, including the control group, received standard physiotherapy that included range of motion exercises and standard nursing care.

Outcome Assessment

All patients had DVT surveillance using fibrinogen iodine I-125 leg scanning and IPG. Leg scanning began on entry to the study and was performed daily for 14 days or until the patient was discharged from the hospital, if earlier. Impedance plethysmography was carried out prior to entry into the study, when possible, and on days 3, 5, 7, 9, 11, and 14 or on the day of discharge from the hospital, if earlier. The results of the tests were interpreted independently by a panel of experts "blinded" to the patient's treatment group. Conflicting interpretations were resolved by consensus. In patients whose IPG or leg scan became abnormal, bilateral ascending venography was performed.

Outcome Events

The principal outcome event was the detection of deep vein thrombosis by fibrinogen iodine I-125 leg scanning or IPG. Calf vein thrombosis was diagnosed if the leg scan was abnormal in the calf only and the IPG was normal. Proximal DVT was diagnosed if the IPG was abnormal or the leg scan was abnormal in the thigh.

Follow-up

Patients were either seen or contacted at three months following discharge from the hospital.

Statistical Analysis

The analysis was based on an intention-to-treat policy whereby outcomes for all randomized patients were included in the final analysis. The frequencies of DVT in the treatment groups were compared using a one-sided χ^2 test or Fisher's exact test.

RESULTS

Patients

Two hundred thirty-nine consecutive eligible patients were randomized to either graduated compression stockings alone (80 patients), to graduated compression stockings plus IPC (78 patients), or to a control group (81 patients). Baseline characteristics are shown in Table 1. The treatment groups were comparable with respect to the variables shown. A total of 66 patients did not have surgery during the study period, and the proportion of patients having surgery was similar in the three treatment groups.

DVT

Seven (8.8%) of the 80 patients randomized to compression stockings alone, seven (9.0%) of the 78 patients randomized to the combined treatment, and 16 (19.8%) of the 81 control patients developed DVT (Table 2). The observed differences among these rates are statistically significant ($P = .028$). Comparing each active treatment group with the control group, the observed differences in the rates of DVT are also statistically significant ($P = .023$ for the graduated compression stockings alone group; $P = .027$ for the combined group). Four of the thrombi were proximal; two of these occurred in the control group and there was one in each of the two active treatment groups.

Of the seven patients in the graduated compression stockings alone group with an abnormal IPG or leg scan, two had ascending venography, both of which were positive for deep vein thrombosis; of the seven patients in the combined treatment group, five had venography, all of which were positive for venous thrombosis; and of the 16 patients in the control group who developed an abnormal IPG or leg scan, 14 had venography, all of which were positive.

Table 1.—Baseline Characteristics*

	Treatment Group		
	Graduated Compression Alone	Graduated Compression Plus IPC	Control
Age, y			
Mean ± SD	49.9 ± 17.78	50.6 ± 18.08	51.0 ± 17.61
Range	16-85	19-86	19-90
Sex, No.			
M	48	46	50
F	32	32	31
Hospital admission diagnosis			
Brain tumor	38	38	38
Spinal cord tumor	0	1	2
Head injury	20	18	19
Spinal cord injury	4	3	4
Subarachnoid hemorrhage	18	18	18
History of DVT			
Yes	1	2	4
No	78	74	75
Not known	1	2	2

*IPC indicates intermittent pneumatic compression; and DVT, deep vein thrombosis.

Table 2.—Frequency of DVT*

Treatment Group	DVT, No. (%)	No DVT	Total
Graduated compression alone	7 (8.8)	73	80
Graduated compression plus IPC	7 (9.0)	71	78
Control	16 (19.8)	65	81
Total	**30**	**209**	**239**

*DVT indicates deep vein thrombosis; and IPC, intermittent pneumatic compression.

Mortality

Eighteen patients died during the 14-day study period; autopsy was performed on seven of them. Ten patients in the graduated compression stockings alone group died, one of whom autopsy showed had PE but whose cause of death was reported to be massive cerebral edema. Four patients in the combined treatment group died and four patients in the control group died, none of whom died of PE.

Patient Tolerance to Graduated Compression Stockings and IPC

Two patients in the graduated compression stockings alone group did not wear the stockings according to the

protocol for the required treatment period, and in one other patient the stockings could only be applied below the knee because of obesity. Ten patients in the graduated compression stockings plus IPC group did not tolerate the treatment for the specified period of time, although eight of these patients wore the graduated compression stockings as required.

Follow-up

One patient in the control group was unavailable for follow-up. At the three-month follow-up, 36 patients were still in the hospital since the beginning of the study, 14 in the graduated compression stockings alone group, ten in the combined group, and 12 in the control group. Nineteen patients died during the follow-up period; autopsy was performed in three. Seven patients in the graduated compression stockings alone group died; none was considered to have PE as a cause of death. Six patients in the combined treatment group died, none of whom had PE as a cause of death.

COMMENT

In this study, 16 (19.8%) of 81 patients in the control group developed DVT, which is consistent with previous studies in these patients. The results of the study demonstrate that either graduated compression stockings alone or the combination of graduated compression stockings and IPC is effective in reducing the incidence of DVT in neurosurgical patients. The observed rates of DVT were similar in the two treatment groups. However, the 95% confidence limit of the true difference of combined treatment over stockings alone was 7%. Hence, the sample size was not sufficient to rule out a clinically important benefit in favor of combined treatment.

There have been few reports on the use of low-dose heparin prophylaxis in neurosurgical patients. Powers and Edwards,[13] in a review of the low-dose heparin studies, concluded that low-dose heparin was indicated in all patients undergoing elective neurosurgical procedures and that the regimen was efficacious and safe. However, the studies were too small to exclude a clinically important bleeding rate, including intracranial bleeding, in the heparin group. Therefore, low-dose heparin is not widely used in these patients. The main attraction of physical methods of prophylaxis in neurosurgical patients is that they are free of the potential for hemorrhagic side effects. In our study, both physical regimens were well tolerated and were found to be highly practical. Seventy-eight (98%) of the 80 patients in the graduated compression stockings alone group and 68 (87%) of the 80 patients in the graduated compression stockings plus IPC group wore the devices according to the protocol. Our study provides strong confirmatory evidence that graduated compression stockings alone are an effective method of prophylaxis in neurosurgical patients. Based on our study, it would be reasonable to recommend that neurologic patients who are undergoing neurosurgical procedures or those who are comatose or paralyzed should have graduated compression stockings with the option of adding IPC until they are fully ambulant. In addition, it would be appropriate to monitor these patients with noninvasive tests for early detection of DVT.

The following neurosurgeons at the Hamilton General Hospital allowed us to study their patients: Rocco A. Devilliers, MD, Ronald A. Dolan, MD, Robert R. Hansebout, MD, Robert D. Hollenberg, MD, Stanley W. Schatz, MD, and John D. Wells, MD.

References

1. Turpie AGG, Gallus AS, Beattie WS, et al: Prevention of venous thrombosis in patients with intracranial disease by intermittent pneumatic compression of the calf. *Neurology* 1977;5:435-438.
2. Skillman JJ, Collins EC, Coe NP, et al: Prevention of deep vein thrombosis in neurosurgical patients: A controlled, randomized trial of external pneumatic compression boots. *Surgery* 1978;83:354-358.
3. Turpie AGG, Delmore T, Hirsh J, et al: Prevention of venous thrombosis by intermittent sequential calf compression in patients with intracranial disease. *Thromb Res* 1979;15:611-616.
4. Turpie AGG, Gent M, Doyle DJ, et al: An evaluation of suloctidil in the prevention of deep vein thrombosis in neurosurgical patients. *Thromb Res* 1985;39:173-181.
5. Sigel B, Ipsen J, Felix WR: The epidemiology of lower extremity deep venous thrombosis in surgical patients. *Ann Surg* 1974;179:278-290.
6. Watson N: Anticoagulant therapy in the treatment of venous thrombosis and pulmonary embolism in acute spinal injury. *Paraplegia* 1974;12:197-201.
7. Turpie AGG, Hirsh J: Venous thromboembolism: II. Current concepts. *Hosp Med*, November 1984, pp 13-41.
8. Holford CP: Graded compression for preventing deep venous thrombosis. *Br Med J* 1976;2:969-970.
9. Scurr JH, Ibrahim SZ, Faber RG, et al: The efficacy of graduated compression stockings in the prevention of deep vein thrombosis. *Br J Surg* 1977;64:371-373.
10. Allan A, Williams JT, Bolton JP, et al: The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. *Br J Surg* 1983;70:172-174.
11. Bergqvist D, Lindblad B: The thromboprophylactic effect of graded elastic compression stockings in combination with dextran 70. *Arch Surg* 1984;119:1329-1331.
12. Colditz GA, Tuden RL, Oster G: Rates of venous thrombosis after general surgery: Combined results of randomized clinical trials. *Lancet* 1986;2:143-146.
13. Powers SK, Edwards MSB: Prophylaxis of thromboembolism in the neurological patient: A review. *Neurosurgery* 1982;10:509-513.

Acute Hyperparathyroidism With Systemic Calcinosis

Report of a Case

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Arnold Silverberg, MD; Robert Frankel, MD;
Jacob Groopman, MD

• **A patient with a huge mediastinal parathyroid adenoma had an acute hypercalcemic crisis. The patient exemplifies the many pitfalls in diagnosis and management of this unusual complication. Postoperatively the patient further developed severe calciphylaxis with calcinosis cutis and systemic and pulmonary calcinosis, a most rare condition.**
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Primary hyperparathyroidism has become a frequently identified condition, often detected by serendipity at the time of routine automated multichannel blood chemis-

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