

## ENOXAPARIN PLUS COMPRESSION STOCKINGS COMPARED WITH COMPRESSION STOCKINGS ALONE IN THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER ELECTIVE NEUROSURGERY

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### ABSTRACT

**Background** Compression stockings are recommended for prophylaxis against venous thromboembolism in patients undergoing neurosurgery, but anticoagulant agents have not gained wide acceptance because of concern about intracranial bleeding.

**Methods** In a multicenter, randomized, double-blind trial, we assessed the efficacy and safety of enoxaparin in conjunction with the use of compression stockings in the prevention of venous thromboembolism in patients undergoing elective neurosurgery. Enoxaparin (40 mg once daily) or placebo was given subcutaneously for not less than seven days beginning within 24 hours after surgery. The primary end point was symptomatic, objectively confirmed venous thromboembolism or deep-vein thrombosis assessed by bilateral venography, which was performed in all patients on day 8±1. Bleeding side effects were carefully assessed.

**Results** Among the 307 patients assigned to treatment groups, 129 of the 154 patients receiving placebo (84 percent) and 130 of the 153 patients receiving enoxaparin (85 percent) had venographic studies adequate for analysis. An additional patient in the placebo group died before venography of autopsy-confirmed pulmonary embolism. In this analysis, 42 patients given placebo (32 percent) and 22 patients given enoxaparin (17 percent) had deep-vein thrombosis (relative risk in the enoxaparin group, 0.52; 95 percent confidence interval, 0.33 to 0.82; P=0.004). The rates of proximal deep-vein thrombosis were 13 percent in patients receiving placebo and 5 percent in patients receiving enoxaparin (relative risk in the enoxaparin group, 0.41; 95 percent confidence interval, 0.17 to 0.95; P=0.04). Two patients in the placebo group died of autopsy-confirmed pulmonary embolism on days 9 and 16. Major bleeding occurred in four patients receiving placebo (intracranial bleeding in all four) and four patients (intracranial bleeding in three) receiving enoxaparin (3 percent of each group).

**Conclusions** Enoxaparin combined with compression stockings is more effective than compression stockings alone for the prevention of venous thromboembolism after elective neurosurgery and does not cause excessive bleeding. (N Engl J Med 1998; 339:80-5.)

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**V**ENOUS thromboembolism is a common, life-threatening complication in patients undergoing elective neurosurgery. An average incidence of deep-vein thrombosis of 24 percent was found among 474 untreated control patients included in eight studies on the prevention of venous thromboembolism in elective (scheduled) neurosurgery.<sup>1-8</sup> Pulmonary embolism has been reported to occur in 1.5 to 5 percent of patients undergoing neurosurgery, with a mortality rate ranging from 9 percent to 50 percent.<sup>9</sup>

The optimal strategy for prophylaxis against venous thromboembolism in elective neurosurgery is unclear. Physical methods, including intermittent-pneumatic-compression devices and compression stockings,<sup>1,2,4-6,8</sup> have been preferred to anticoagulant agents because of concern about intracranial bleeding.<sup>10</sup> Compression stockings and intermittent pneumatic compression have been shown to be equally effective.<sup>8,11</sup> For this reason, and because of the inconvenience and costs of devices providing intermittent pneumatic compression, compression stockings are the most commonly used prophylactic measure for venous thromboembolism in patients undergoing neurosurgery.<sup>9,10</sup> However, the majority of studies evaluating physical methods in the prevention of deep-vein thrombosis in neurosurgery have used noninvasive screening tests with low sensitivity, such as radioactive fibrinogen scanning.<sup>12</sup> In the only neurosurgery trial in which deep-vein thrombosis was assessed by bilateral venography, compression stockings were associated with an incidence of deep-vein thrombosis of 26 percent.<sup>13</sup>

In this multicenter, randomized, double-blind trial, we compared the use of compression stockings alone with the use of compression stockings plus the administration of the low-molecular-weight heparin enoxaparin for the prevention of venous thrombo-

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embolism in patients undergoing neurosurgery. Enoxaparin was started on the morning after neurosurgery, within 24 hours after the completion of the operation. It was not started sooner because of the possibility of bleeding in patients who had undergone operation for extensive tumors. Starting enoxaparin after surgery was considered appropriate because studies in high-risk surgical settings have demonstrated a significant reduction in postoperative venous thromboembolism without excessive bleeding when anticoagulant agents are started after surgery.<sup>14-17</sup> The principal outcome measure was symptomatic, objectively confirmed venous thromboembolism or deep-vein thrombosis as assessed by mandatory bilateral venography performed on day  $8 \pm 1$ . Because the use of anticoagulants in patients undergoing neurosurgery may be associated with a high risk of bleeding, we also assessed the safety of enoxaparin in this clinical setting.

## METHODS

### Study Patients

Consecutive patients 18 years of age or older, with a body weight between 40 and 120 kg, who were undergoing elective cranial or spinal surgery were assessed to determine their eligibility for the study. Patients were excluded if they had abnormal operative bleeding or bleeding disorders (defined by a prothrombin time more than 30 percent longer than the control value or a platelet count of less than 100,000 per cubic millimeter), needed therapeutic anticoagulant or antiplatelet agents, could not undergo venography because of allergy to contrast material, had renal failure (defined by a serum creatinine level higher than 2 mg per deciliter [ $180 \mu\text{mol}$  per liter]), were likely to remain in the hospital for less than seven days, were pregnant, or refused consent. The study protocol was approved by the institutional review boards of the participating hospitals.

### Study Design and Interventions

On the morning after neurosurgery, eligible patients were randomly assigned by a computer-derived protocol to receive either enoxaparin (Clexane, 100 anti-factor Xa units per milligram; Rhone-Poulenc Rorer, Milan, Italy) at a dose of 40 mg per day or placebo. Enoxaparin and placebo were given as 0.4-ml subcutaneous injections once daily with preloaded syringes. The protocol specified that the first dose of study medication be given within 24 hours after surgery and that the treatment be continued for  $8 \pm 1$  days. Thigh-length compression stockings (TED, Kendall Healthcare Products, Mansfield, Mass.) were put on all patients on the morning of surgery and were worn until discharge. No physical or pharmacologic methods of antithrombotic prophylaxis other than compression stockings and enoxaparin were permitted. Concomitant treatment with aspirin, other antiplatelet agents, or nonsteroidal antiinflammatory drugs was not permitted during the trial.

The clinical trial was carried out in seven Italian neurosurgery centers. The coordinating and methods center was located at the Istituto di Medicina Interna e Medicina Vascolare, University of Perugia, Perugia, Italy.

### Surveillance Program and Follow-up

The participating patients were assessed daily during the hospital stay to ensure compliance with the protocol and to review their clinical status, including symptoms and signs of venous thromboembolism, bleeding side effects, and other adverse events. Patients in whom deep-vein thrombosis was clinically suspected

underwent real-time B-mode compression ultrasonography, followed, if the results were positive, by venography. If the ultrasound examination was negative, the patient continued in the trial until the scheduled venographic examination at the end of the treatment period. Patients with clinical features suggestive of pulmonary embolism were scheduled to undergo ventilation-perfusion lung scanning. A normal perfusion scan was considered to rule out pulmonary embolism, whereas a scan indicating a high probability of embolism, defined as a scan showing one or more segmental or larger perfusion defects with relatively preserved ventilation, was considered to confirm the diagnosis. Patients with nondiagnostic lung scans were scheduled to undergo venous ultrasonography of the legs, followed, if the results were negative, by pulmonary angiography.

The participating patients were followed by means of hospital visits or telephone calls until 60 days after surgery to document the occurrence of clinically overt venous thromboembolism, bleeding, or death. No further pharmacologic prophylaxis against venous thromboembolism was given in patients with negative venographic results. Patients with positive venographic results were treated with unfractionated heparin, low-molecular-weight heparins, warfarin, or vena caval filters, as appropriate.

### End Points

The primary end point was symptomatic, objectively documented venous thromboembolism (deep-vein thrombosis or pulmonary embolism) or deep-vein thrombosis detected by bilateral venography performed at the end of the treatment period. Venography was performed with a non-ionic contrast agent according to the technique of Rabinov and Paulin on day  $8 \pm 1$ , or earlier in patients in whom a clinical suspicion of deep-vein thrombosis was confirmed by real-time B-mode ultrasonography.<sup>18</sup> Deep-vein thrombosis was defined as a constant intraluminal filling defect in a deep leg vein that was seen on two or more views or after a second injection of contrast material. Deep-vein thrombosis was classified as proximal or distal. Proximal deep-vein thrombosis was defined as thrombosis involving the popliteal or more proximal veins. Symptomatic pulmonary embolism was confirmed by high-probability ventilation-perfusion lung scanning, pulmonary angiography, or autopsy.

Bleeding was considered major and resulted in withdrawal of treatment when it was clinically overt and associated with a decrease in the hemoglobin level of at least 2 g per deciliter or with the transfusion of two or more units of packed cells. Intracranial and retroperitoneal bleeding, as well as bleeding requiring surgical intervention, was also considered major. All other bleeding was considered minor.

Venograms and lung scans were evaluated by a central panel unaware of the clinical data, the treatment assignment, or the attending physician's interpretation of the venogram and lung scan. The data on bleeding were also reviewed by a central panel unaware of treatment assignment. The adjudicating panel classified all deaths as due to bleeding, pulmonary embolism, or other causes. To analyze the cause of death and the data on bleeding, the adjudicating panel had all relevant information available, including cerebral computed tomographic scans, nuclear magnetic resonance images, and pathology reports.

### Statistical Analysis

The efficacy analysis compared the combined rates of symptomatic, objectively confirmed venous thromboembolism and deep-vein thrombosis detected by screening venography between the patients receiving placebo and those receiving enoxaparin.

The safety analysis compared the rates of bleeding between the placebo and enoxaparin groups. All patients assigned to treatment were included in the safety analysis. Death within 60 days after the start of treatment and other adverse events were also analyzed.

The calculation of sample size was based on an expected incidence of deep-vein thrombosis of 30 percent in the control

group<sup>13</sup> and of 15 percent in the enoxaparin group. Approximately 300 patients would be needed to detect this clinically important 50 percent difference with an alpha level of 0.05 (two-tailed) and a beta level of 0.20, assuming that adequate venographic studies would be available for 80 percent of the enrolled patients.

The rates of venous thromboembolic events and bleeding were compared with use of Fisher's exact test.<sup>19</sup> The P values are two-sided. The incidence rates of thromboembolic events in the two groups were also compared with use of the Cochran-Mantel-Haenszel chi-square test with adjustment for center, after centers with fewer than 30 patients had been pooled, and for the site of surgery (intracranial or spinal).

## RESULTS

During the study period, 661 patients were admitted to the study centers for neurosurgery and assessed for eligibility for the study. A total of 354 patients (54 percent) were excluded from the study for the following reasons: informed consent was not obtained (255 patients), there was abnormal operative bleeding (39 patients), they had bleeding disorders (20 patients), they were receiving concomitant treatment with anticoagulant or antiplatelet agents (19 patients), the expected hospital stay was less than seven days (14 patients), or they were allergic to venographic contrast material (7 patients).

Of the 307 eligible patients, 154 were randomly assigned to receive placebo and 153 to receive enoxaparin (Table 1). The groups were well balanced with respect to demographic characteristics as well as presurgery mobility, hospital stay before surgery, duration of surgery, reasons for surgery, and tumor histology. More patients receiving enoxaparin than control patients had spinal surgery. Two hundred ninety-nine patients had surgery for brain or spinal tumors. The reasons for surgery in the remaining eight patients were cerebral aneurysm, vertebral-disk displacement, and gliosis. The length of time between surgery and the first dose of enoxaparin or placebo ranged from 12 to 24 hours. The mean duration of treatment was  $8.7 \pm 1.3$  days in both groups.

Among the 307 patients in the study, 259 (84 percent) had venographic studies that were adequate for analysis (84 percent of the placebo group and 85 percent of the enoxaparin group). Twenty-four patients in the placebo group and 23 patients in the enoxaparin group did not undergo venography, for the reasons shown in Table 2. Among these patients, 13 in the placebo group and 9 in the enoxaparin group completed treatment.

### Venous Thromboembolism

One patient in the placebo group died before venography (on day 9) because of pulmonary embolism confirmed by autopsy. The overall prevalence of deep-vein thrombosis (proximal and distal) among those who had adequate venographic studies was 33 percent (42 of 129 patients) in the placebo group and 17 percent (22 of 130 patients) in the enoxaparin group ( $P=0.004$ ). The respective rates of

**TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE 307 PATIENTS INCLUDED IN THE STUDY.\***

CHARACTERISTIC	PLACEBO (N=154)	ENOXAPARIN (N=153)
Age — yr	57.5±12.1	55.1±13.7
Male sex — no. of patients (%)	84 (55)	69 (45)
Weight — kg	70.3±10.9	70.7±13.9
Presurgery mobility — % of patients		
Normal	63	62
Reduced	37	38
Hospitalization before surgery — days	10.5±8.4	9.5±7.3
Duration of surgery — hr	4.7±1.9	4.7±2.1
Site of surgery — no. of patients (%)		
Intracranial	139 (90)	122 (80)
Spinal cord	15 (10)	31 (20)
Reason for surgery — no. of patients (%)		
Tumor	150 (97)	149 (97)
Non-neoplastic disease	4 (3)	4 (3)
Tumor histology — no. of patients (%)		
Meningioma	63 (42)	61 (41)
Glioma	43 (29)	42 (28)
Sheath tumors	11 (7)	14 (9)
Carcinoma metastasis	12 (8)	8 (5)
Other	21 (14)	24 (16)

\*Plus-minus values are means ±SD.

**TABLE 2. PATIENTS INCLUDED IN THE EFFICACY ANALYSIS.**

CATEGORY	PLACEBO	ENOXAPARIN
	no. of patients	
Randomized	154	153
Included in the efficacy analysis	130	130
Adequate venographic studies	129	130
Pulmonary embolism confirmed by autopsy	1	0
Venography not performed	24	23
Venography impossible	14	10
Withdrawal due to bleeding	3	6
Death	1	2
Withdrawal of consent	3	2
Improper inclusion	3	3

proximal deep-vein thrombosis were 13 percent (17 of 129 patients) and 5 percent (7 of 130 patients) ( $P=0.04$ ). Among the 260 patients with adequate venograms or confirmed pulmonary embolism, the relative risk with enoxaparin as compared with placebo was 0.52 (95 percent confidence interval, 0.33 to 0.82) for overall deep-vein thrombosis and 0.41 (95 percent confidence interval, 0.17 to 0.95) for proximal deep-vein thrombosis (Table 3). After adjust-

**TABLE 3. RATES OF DEEP-VEIN THROMBOSIS AND PULMONARY EMBOLISM IN PATIENTS RECEIVING PLACEBO OR ENOXAPARIN.\***

EVENT	PLACEBO (N=130)	ENOXAPARIN (N=130)	P VALUE†	RELATIVE RISK (95% CI)
	no. of patients (%)			
PE or DVT	43 (33)	22 (17)	0.004	0.51 (0.33–0.80)
PE or proximal DVT	18 (14)	7 (5)	0.04	0.39 (0.17–0.90)
Overall DVT	42 (32)	22 (17)	0.004	0.52 (0.33–0.82)
Proximal DVT	17 (13)	7 (5)	0.04	0.41 (0.17–0.95)
PE	1 (1)	0		

\*CI denotes confidence interval, PE pulmonary embolism, and DVT deep-vein thrombosis. The placebo group included 129 patients with adequate venographic studies and 1 who died of pulmonary embolism, confirmed at autopsy, before venography could be performed.

†P values were calculated with use of Fisher's exact test.

ment for the center and the location of surgery (intracranial or spinal), the relative risk with enoxaparin was 0.54 (95 percent confidence interval, 0.35 to 0.84; P=0.007) for overall deep-vein thrombosis and pulmonary embolism and 0.40 (95 percent confidence interval, 0.17 to 0.94; P=0.04) for proximal deep-vein thrombosis and pulmonary embolism.

**Clinically Overt Thromboembolic Events**

During the 60-day study period, nine patients in the placebo group (6 percent) and one in the enoxaparin group (1 percent) had clinically overt thromboembolic events confirmed by objective testing. Five patients in the placebo group and one in the enoxaparin group had deep-vein thrombosis confirmed by venography during the hospital stay. One patient assigned to placebo, who had asymptomatic distal deep-vein thrombosis on pre-discharge venography, had symptomatic proximal deep-vein thrombosis, confirmed by ultrasonography, one month after discharge.

Three patients assigned to placebo presented with symptoms and signs of pulmonary embolism. Two of these patients died of pulmonary embolism, as confirmed by autopsy, on days 9 and 16. In the other patient, the suspicion of pulmonary embolism was confirmed by objective testing on day 18. Both patients who had pulmonary embolism after day 10 had proximal deep-vein thrombosis on pre-discharge venography. No clinically overt thromboembolic events were observed in patients discharged from the hospital with negative venographic results.

**Bleeding**

As shown in Table 4, major bleeding occurred in four patients assigned to placebo (3 percent) and four assigned to enoxaparin (3 percent). The major bleeding was intracranial in all four patients assigned

**TABLE 4. MAJOR AND MINOR BLEEDING IN STUDY PATIENTS.**

EVENT	PLACEBO (N=154)	ENOXAPARIN (N=153)	P VALUE*
	no. of patients (%)		
Major and minor bleeding	11 (7)	18 (12)	0.18
Major bleeding	4 (3)	4 (3)	
Intracranial bleeding	4	3	
Melena with anemia	0	1	
Minor bleeding	7 (5)	14 (9)	
Surgical-wound hematoma	2	8	
Hematuria	3	1	
Injection-site hematoma	0	2	
Anemia without clinically overt bleeding	2	3†	

\*The P value was calculated with use of Fisher's exact test.

†Treatment was discontinued in two patients.

to placebo and in three of the patients assigned to enoxaparin. The remaining case of major bleeding in the enoxaparin group was melena with anemia. In two patients in the enoxaparin group, treatment was discontinued because of anemia without overt bleeding. In the enoxaparin group a higher incidence of minor bleeding was observed, primarily because of mild surgical-wound and injection-site hematomas not requiring blood transfusion (Table 4).

**Deaths**

Eleven patients died during the 60-day study period: six in the placebo group (4 percent) and five in the enoxaparin group (3 percent). During the first 10 days, two patients died in each group. One patient in the placebo group died of pulmonary embolism, confirmed by autopsy, and the other three patients died of nonhemorrhagic cerebral complications. From day 10 to day 60, four patients in the placebo group and three in the enoxaparin group died. In the placebo group, one patient died of pulmonary embolism confirmed by autopsy on day 16, one of a nonhemorrhagic cerebral complication, one of tumor progression, and one of unknown causes. In the enoxaparin group, the deaths were due respectively to nonhemorrhagic cerebral complication, cardiorespiratory failure, and unknown causes. The patient assigned to placebo who died of late pulmonary embolism had proximal deep-vein thrombosis according to pre-discharge venography.

**Other Adverse Events**

One patient in the placebo group and two in the enoxaparin group had thrombocytopenia, as defined by a platelet count of less than 100,000 per cubic millimeter and a decrease of at least 50 percent from

the pretreatment values. None of the patients who had thrombocytopenia had venous or arterial thrombosis.

### DISCUSSION

Our results show that the low-molecular-weight heparin enoxaparin, used in conjunction with compression stockings, reduced the rate of venous thromboembolism from 33 percent (the rate observed with compression stockings alone) to 17 percent, for a relative risk of 0.51. The lower limit of the confidence interval for the reduction in the relative risk was 0.20, which exceeds the minimal level indicating a clinically important benefit.<sup>20</sup> The rate of proximal deep-vein thrombosis or pulmonary embolism was reduced from 14 percent to 5 percent, for a relative risk of 0.39.

The 17 percent rate of venous thromboembolism that we observed despite prophylaxis with enoxaparin is probably due to the combination of a powerful thrombogenic stimulus in patients with brain or spinal tumors, who represented 97 percent of the study population, and the delay between surgery and the start of prophylaxis. The majority of the residual thrombi were located in the calf veins. The clinical significance of calf thrombi in patients undergoing neurosurgery is unknown, but such thrombi should not be ignored, since thrombi could extend proximally to cause pulmonary embolism. Although it is conceivable that starting prophylaxis before surgery or increasing the dose of enoxaparin might further reduce the incidence of deep-vein thrombosis, bleeding side effects would probably limit the feasibility of these options. The relative advantages of enoxaparin and unfractionated heparin with respect to efficacy and safety remain to be defined in a comparison trial.

The proportion of patients undergoing spinal surgery was lower in the placebo group (10 percent) than in the enoxaparin group (20 percent). We evaluated the potential effect of this difference on the study outcome by including the site of surgery (intracranial or spinal) in the analysis. The results indicate that the difference between the treatment groups in the anatomical location of the surgery had a negligible effect on the outcome of the study.

Intracranial bleeding occurred in four patients given placebo and three patients given enoxaparin. It should be noted that the study had enough power to detect differences in efficacy but was not of adequate size to address differences in the risk of bleeding between the two groups. Therefore we cannot rule out clinically important differences in bleeding. Moreover, patients with excessive operative bleeding and potential risk factors for bleeding were excluded from the study, as were patients undergoing neurosurgery for cerebral trauma. There were more episodes of minor bleeding in the enoxaparin group, al-

most all of them surgical-wound and injection-site hematomas that did not require blood transfusion.

No clinically overt thromboembolic events were observed at follow-up in patients discharged from the hospital with negative venographic studies. This result confirms similar findings in high-risk orthopedic surgery<sup>21,22</sup> and suggests that most late-presenting deep-vein thrombi probably develop in the hospital and become symptomatic after discharge. These data have implications for the optimal duration of prophylactic anticoagulant therapy for venous thromboembolism. However, it should be kept in mind that our results were obtained in patients with negative venographic studies at discharge, whereas in clinical practice most patients are discharged from the hospital without having venography performed.

In summary, our study shows that enoxaparin combined with compression stockings is more effective than compression stockings alone in preventing venous thromboembolism after elective neurosurgery. Although the trial was not sufficiently large to address differences in the risk of bleeding between the two study groups, we found intracranial bleeding, the most feared complication of prophylactic anticoagulant therapy in patients undergoing neurosurgery, to be uncommon and of similar frequency in the placebo and enoxaparin groups. Our findings suggest that compression stockings, together with enoxaparin (40 mg once daily, starting within 24 hours after surgery), should be the method of choice for prophylaxis against venous thromboembolism in the majority of patients undergoing elective neurosurgery.

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### APPENDIX

Other study investigators were as follows: Divisione di Neurochirurgia, Ospedale Silvestrini, and Istituto di Medicina Interna e Medicina Vascolare, Università di Perugia, Perugia: P. Orvieto, G. Ghetti, M. Nardi, D. Arcamone, C. Fioroni, and N. Baffà; Divisione di Neurochirurgia, Ospedale Galliera, Genoa: D. Zerbi; Divisione di Neurochirurgia, Servizio di Coagulazione, Servizio di Neuroranimazione, Ospedale S. Raffaele, Milan: M. Giovannelli, E. Giugni, L. Tomassini, and A. De Vitis; Divisione di Neurochirurgia, II Servizio Radiologia, Azienda Ospedaliera, Parma: S. Pasetti and P. Larini; Divisione di Neurochirurgia, Istituto di Ematologia, Ospedale L. Molinette, Turin: M. Bazzan; and Divisione di Neurochirurgia, Istituto di Patologia Medica II, Università di Padova, Padua: P. Prandoni, M. Marcelli, and P. Bagatella — all in Italy.

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