
Effect of Optimization of Hemodynamics on Fibrinolytic Activity and Antithrombotic Efficacy of External Pneumatic Calf Compression

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External pneumatic calf compression is effective but imperfect for antithrombotic prophylaxis in surgical patients. In preliminary studies, sequential filling of multisegmented leggings with graded pressure decreasing from ankle to knee increased venous flow velocity and wall shear stress, decreased residual venous volume, and enhanced postoperative fibrinolysis more than uniform compression. To determine if improved hemodynamics also increased antithrombotic activity, we performed a prospective randomized trial in neurosurgical patients comparing sequential application of graded pressure with uniform pressure applied to either a segmented bladder or to a single bladder. Deep vein thrombosis was diagnosed by leg scanning and impedance plethysmography and confirmed by phlebography. Venous thrombosis developed in 3 of 45 patients with graded-sequential filling, 6 of 50 with uniform compression-multiple compartments, and 3 of 41 with uniform pressure single bladder (differences not significant). These results suggest either that uniform compression offers all that can be expected of external pneumatic calf compression in prevention of venous thrombosis, or that even if a study with greater statistical power showed graded-sequential filling to be superior, the benefit/cost ratio of the more complex latter system is not likely to be large.

ALTHOUGH THE INCIDENCE of deep vein thrombosis in postoperative patients can be reduced by prophylactic administration of antithrombotic drugs, such preventive measures have not been universally adopted into practice. Several surveys¹⁻³ have reported that many practitioners use prophylactic antithrombotic drugs only in their highest risk patients, if they use them at all. The efficacy of prophylactic administration of anticoagulants and antiplatelet agents is disputed, and is certainly not absolute; failures do occur.

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The requirement for laboratory control, at least with warfarin, is also a deterrent. The most prominent obstacle to wider adoption of antithrombotic prophylaxis, however, has been the fear of bleeding complications, which inevitably to some degree attend the use of antithrombotic drugs in surgical patients.

An alternative approach, attractive because of its freedom from hemorrhagic side effects, is the use of physical methods to reduce pooling of venous blood in the lower extremities and to increase the velocity of venous blood flow. Such physical techniques include elastic stockings, passive leg exercises, electrical calf stimulation, and external pneumatic compression of the legs. The latter has been most extensively studied and appears to be most effective among the physical methods available.

A substantial literature has developed regarding the use of external pneumatic compression boots or leggings in patients at risk of venous thromboembolism, including patients undergoing neurologic operations,⁴⁻⁶ urologic surgery,^{7,8} general surgical procedures for malignant or benign disease,^{9,10} operations for gynecologic malignancy,¹¹ orthopedic procedures,^{12,13} and nonoperative conditions.¹⁴ The mechanism of action of external pneumatic compression in reducing the rate of venous thrombosis in the lower limbs is conjectured to be twofold: a fluid mechanical effect expelling blood from the lower extremities to substitute for the action of the inoperative muscle pump in the recumbent patient, and enhancement of fibrinolytic activity.¹⁵ The relative in-

fluence of these two factors is not certain. External pneumatic compression appears to be associated with no bleeding complications even in patients undergoing extensive surgery.

Although external pneumatic compression of the legs has proven efficacious in reducing the rate of venous thrombosis, there are occasional failures associated with its use, particularly in high risk patients. In our trial of calf compression in neurosurgical patients,⁴ for example, 9% of patients who were treated with external pneumatic compression developed deep vein thrombosis (compared with 25% in the control group). As conventionally applied, external pneumatic calf compression may not produce an optimal hemodynamic effect. It is possible that an improvement in the fluid mechanical aspects of the procedure, brought about by modifications in the apparatus, would be reflected in an increase in its antithrombotic effectiveness.

Shapiro and associates have conducted an extensive study of the hydrodynamics of external pneumatic compression, first in theoretical and experimental circulation models¹⁶ and later in human volunteers using gated blood pool scans of the lower extremities.¹⁷ They compared the amount and rate of blood expelled when different modes of intermittent external pneumatic compression were applied to the lower extremities. Scintillation camera imaging of the labelled red cell pool synchronized to the pressurization cycle provided data on the time course of changes in regional blood volumes in the leg. They calculated regional values of the fraction of blood ejected as well as comparative indices proportional to flow rate, blood velocity, and wall shear stress, all of which might reasonably be regarded as figures of merit to be maximized in an attempt to obtain optimal prophylaxis against deep vein thrombosis. Using a four-compartment cuff, they studied compression modes with different intercompartmental pressure gradations and different intercompartmental intervals to the onset of pressurization. The most effective system hemodynamically was found to be a four-compartment legging in which the bladders filled in sequence beginning at the ankle with graded pressures decreasing from ankle to knee. The optimal values for a four-compartment system were approximately 60, 50, 40, and 30 mmHg, decreasing from ankle to knee, with about 0.25 sec between pressurizations of successive segments, a pressure rise time of less than 0.5 sec, each segment held at full pressure for about 10 sec, and a period of about 50 sec with pressure relieved before the next cycle. No commercially available system is hemodynamically optimal or conforms to these features.

We tested the hypothesis that an external pneumatic compression device with these characteristics would improve antithrombotic efficacy in patients undergoing

neurosurgical operations, a high-risk group that cannot safely be given antithrombotic drugs because of the hazard of intracranial bleeding complications. A corollary of this hypothesis would be that graded-sequential filling of such a specially designed apparatus would have sufficiently improved antithrombotic properties to justify its increased cost and complexity. We also studied the effect of different modes of calf compression on whole blood fibrinolytic activity to explore further the mechanism of the antithrombotic action of external pneumatic compression.

Methods

The trial was initiated as a two-armed clinical study with randomization afforded by a series of sealed envelopes. Patients were assigned either to receive uniform compression delivered by a four-compartment system applied to the calf (Group II), with all compartments filled simultaneously to the same pressure, or to have sequential filling of the same system from ankle to knee with graduated pressure decreasing from ankle to knee (Group I) according to specifications derived from the studies of Kamm et al.¹⁷ with pressure and timing values as stated above. The apparatus was furnished by Gaymar Industries, Inc., Orchard Park, NY. The four-segment cuffs had "wavy" boundaries between segments, a configuration that effectively eliminated the pooling of blood that, in the scintillation studies of Kamm et al., had been observed to occur between segments of more conventional four-segment cuffs.

The study was conducted in patients undergoing neurosurgical operations at the Beth Israel Hospital. A description of the patient population is presented in Table 1. External pneumatic compression was applied during the induction of anesthesia, except for two patients (1 in Group I and 1 in Group II) in whom confinement to bed before operation suggested the need for earlier prophylaxis. In these cases the external pneumatic compression device was applied as soon as the patient came to the attention of the investigators.

Diagnosis of deep vein thrombosis was made by ¹²⁵I-fibrinogen scanning,¹⁸ which was begun on the first post-operative day, impedance plethysmography (IPG)¹⁹ every second day, and ascending phlebography by the technique of Rabinov and Paulin²⁰ in patients who had positive fibrinogen scans or IPGs. In addition, blood was drawn before operation and at intervals in the postoperative period for determination of fibrinolytic activity in heparinized whole blood by a radioactive clot lysis technique modified by Coppe et al.²¹ from the method of Moroz.²² General surgical patients undergoing operations for nonthrombotic conditions were also studied as controls for the fibrinolysis assay. Patients were main-

TABLE 1. Patient Groups

	Group I Graded- Sequential	Group II Uniform Pressure, Four Compartment	Group III Single Bladder
No. of patients	45	50	41
Sex (M/F)	24/21	23/27	20/21
Age			
10-20	0	0	0
21-30	9	4	6
31-40	10	8	4
41-50	8	16	8
51-60	8	8	8
61-70	6	5	8
71-80	2	8	7
>80	2	1	0
Surgical procedure			
Craniotomy for tumor	4	6	5
Shunts	6	5	5
Other craniotomies	9	9	5
Cervical laminectomy	7	9	8
Lumbar laminectomy	13	14	12
Spinal fusion	6	7	6
Risk factors for DVT			
Previous DVT or PE	4	1	2
Obesity	10	8	10
Varicose veins	3	2	2
EACA	1	0	0

tained on external pneumatic compression until they became ambulatory or for a maximum of the period spanned by three injections of labelled fibrinogen, roughly 3 weeks.

After 43 patients had been entered into the trial, Group III, receiving uniform compression with a single bladder system (Venodyne, Lyne-Nicholson, Inc.), was added to provide a realistic comparison of graded-sequential filling *versus* a commercially available system having uniform pressurization. The randomization was adjusted to balance the three patient groups. It should be noted that the Venodyne system has a substantially longer pressure rise time than do the other systems studied.

For ethical reasons no unprotected control group was included in this study, which instead compared a technique of established effectiveness *versus* another form of treatment that was potentially superior. This protocol was approved by the Institutional Review Board at the Beth Israel Hospital.

Results

One hundred fifty-eight subjects were enrolled in the study, but 22 were dropped prior to its completion because of nonadherence to the study protocol in 13 patients, including two who refused the procedure because of discomfort, nonoperative therapy (5 patients), or fail-

ure of the apparatus (4 patients). Forty-five of the remaining 137 patients were in Group I, 50 in Group II, and 41 in Group III. The surgical procedures, age, sex, and other relevant clinical details are shown in Table 1. The groups appeared to be comparable in all important respects, except that patients in Group I had a somewhat higher prevalence of risk factors for venous thrombosis.

Compression of the limbs is known to enhance systemic fibrinolytic activity, which might augment the antithrombotic action of external pneumatic compression. We studied whole blood fibrinolytic activity in the first 75 patients. A fall in fibrinolytic activity is characteristic of postoperative patients, beginning in the first 24 hours after operation and reaching its nadir by the third postoperative day.^{23,24} Such a reduction in fibrinolytic activity was exhibited by the group of general surgical patients studied as controls (Fig. 1; $p < 0.01$ preop vs. postop day 1, Friedman's rank sum test). Patients who received external pneumatic compression of the limbs with a uniform compression device, either in Group II or Group III, failed to display this expected fall in fibrinolytic activity in the postoperative period and, in fact, 9 of 16 patients (56%) with the single bladder system and 21 of 35 (60%) with the four-compartment uniform compression system showed an *increase* in the fibrinolytic index on the first postoperative day (Figs. 1 and 2).

Patients in Group I had an average increase in fibrinolytic activity that was significantly greater in magnitude than for those in Groups II and III (mean fibrinolytic index on first postop day 1.45 for graded sequential group vs. 1.06 for single bladder system and 1.12 for multiple bladder system with uniform compression; $p < 0.02$ by Dunnett's test or Kruskal-Wallis test), and 23 of 25 patients (92%) with graded sequential filling had a rise in activity. Thus the effect on fibrinolytic activity was correlated with the hemodynamic effectiveness of the external pneumatic compression systems. Patients who failed to be protected by external pneumatic compression, and who developed venous thrombosis despite its use, typically also failed to develop enhanced fibrinolytic activity as a result of the application of external pneumatic compression after operation. Six of the eight such patients whose fibrinolytic index was assessed on the first postop day had values below their group mean (Fig. 2). Patients whose level of fibrinolytic activity was increased did not exhibit any clinically obvious bleeding tendency as a result, but blood loss was not measured and this issue was not rigorously appraised.

The effect of the treatments on the incidence of deep venous thrombosis is shown in Table 2. All patients who developed a positive fibrinogen scan or IPG were requested to have a phlebogram to confirm the diagnosis of venous thrombosis, but five refused. Fifteen patients developed a positive fibrinogen scan; ten of these had a

phlebogram, three of which proved to be negative. These three patients are regarded as "false positives," although the positive scan may have been related to venous thrombosis in a muscular tributary of the deep venous system that was not visible on phlebography. For purposes of analysis, "positive" patients are considered to be those who have a positive scan with a positive (confirmatory) phlebogram plus those who had a positive scan but did not have a phlebogram.⁴ The results of such an analysis suggest a trend toward a greater antithrombotic effect for graded sequential filling than for the uniform pressure four-compartment system, but no difference from the single bladder uniform compression system. The differences are not statistically significant. The 95% confidence interval for the difference between graded sequential compression and uniform compression with multiple segments is from -16.9% to 6.3%, and for the difference between graded sequential compression and uniform compression with a single bladder it is from -11.4% to 10.2%. The fact that these intervals include zero is consistent with the lack of statistical significance.²⁵

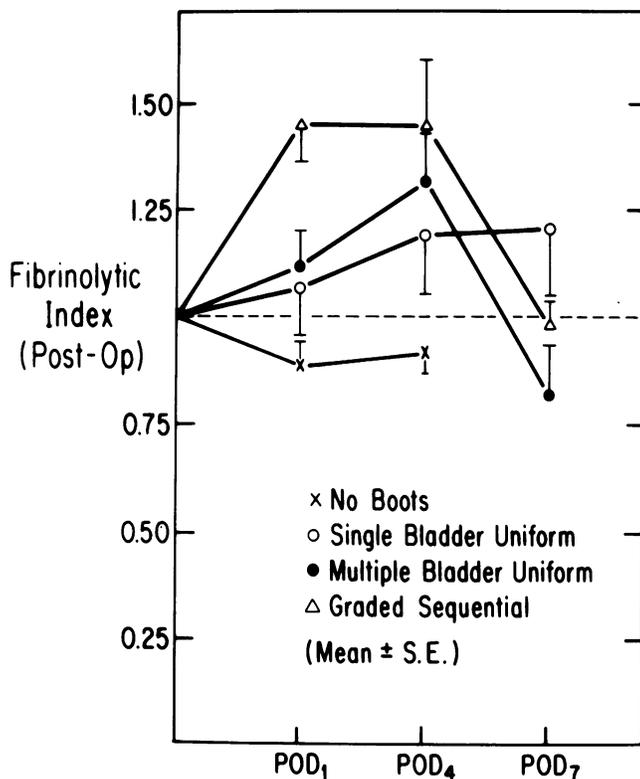


FIG. 1. Fibrinolytic activity in the three patient groups on the first, fourth, and seventh postoperative days. Analogous values are also shown for general surgical patients undergoing operations of comparable severity ("no boots"). Results are expressed as a "fibrinolytic index" (cpm released into supernatant divided by cpm originally contained in radioactive clot) and are normalized to preoperative values for each patient.

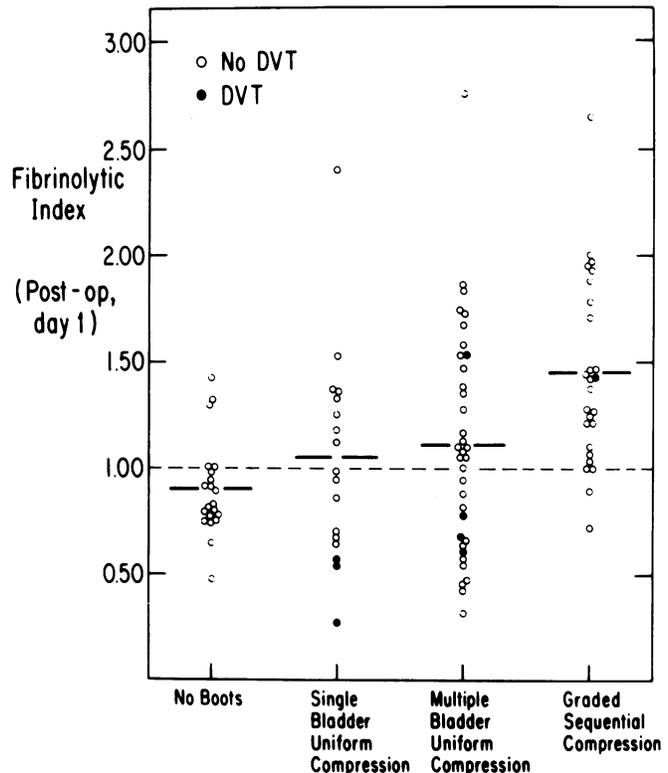


FIG. 2. Fibrinolytic index on the first postoperative day in the four patient groups. Horizontal bars indicate mean values. Closed circles indicate patients who subsequently developed deep vein thrombosis.

The same conclusion will be reached if one considers as "positive" only those patients who had a positive scan with a positive (confirmatory) phlebogram or if one includes as positive all patients with a positive scan regardless of the phlebogram.

We calculated that if the present rate of venous thrombotic complications were maintained, approximately 500 patients in each group would be required to show a statistically significant difference between Group I and the other groups with an alpha error <0.05 and a beta error of 0.20.²⁶ Because this was considered impractical the study was terminated at this time.

Discussion

External pneumatic compression is an established form of prophylaxis for prevention of venous thrombosis in postoperative patients. The relative importance of enhanced fibrinolysis and of physical dispersion of the components of a thrombus by hemodynamic factors in calf compression is not known. In this study they tended to vary together. The failure of fibrinolytic activity to be enhanced by pneumatic compression in patients who subsequently developed venous thrombosis was predictable. The association of long whole blood clot lysis times with subsequent venous thrombosis in surgical patients

TABLE 2. Deep Vein Thrombosis

	Group I Graded Sequential Compression	Group II Uniform Pressure, Multiple Compartment	Group III Uniform Pressure, Single Bladder
N	45	50	41
A. + scan + venogram	2	3	2
B. + scan no venogram	1	3	1
C. + scan - venogram	0	2	1
DVT: A + B	3/45 (6.7%)	6/50 (12%)	3/41 (7.3%)
A + B + C	3/45 (6.7%)	8/50 (16%)	4/41 (9.8%)
A only	2/45 (4.4%)	3/50 (6%)	2/41 (4.9%)
Development of DVT, postop days	2, 4, 7	1, 2, 5, 5, 12, 13	2, 2, 3
DVT, (A + B), operation	Craniotomy for tumor Laminectomy (2)	Craniotomy for tumor (2) Craniotomy for trauma Other craniotomy (2) Laminectomy	Craniotomy for tumor Laminectomy Harrington rod

was observed by Comp and associates,²⁷ and Clayton et al.²⁸ found low levels of fibrinolytic activity to be a sensitive predictor of venous thrombosis in patients undergoing gynecologic operations.

The evidence for the efficacy of pneumatic compression is persuasive, but calf compression might be even more effective if its hemodynamic effects were optimized. Among the four fluid mechanical parameters influenced by external pneumatic compression (flow velocity, volume flow rate, shear stress, and residual volume of blood in the limbs), it is not yet possible to decide which is most important for antithrombotic effectiveness of the system; however, since under normal circumstances they all tend to vary together, this point may be moot. It is clear that commercially available systems for applying external pneumatic compression to the lower limbs are not optimized in these respects.

We found that a system for external pneumatic compression in which the pressure was applied in a graded fashion, milking the blood from ankle to knee, was more effective hemodynamically, and in the clinical trial it proved to be more effective in enhancement of fibrinolytic activity than uniform compression applied to the leg either in a multiple bladder system or in a single bladder. Nicolaides et al.²⁹ have previously reported that a multiple bladder system involving sequential filling from ankle to thigh but with uniform pressure was more effective in accelerating femoral venous flow and was superior to a single bladder system in preventing proximal venous thrombosis in patients undergoing abdominal operations; however, there was no significant difference in the rate of calf thrombi. Since the sequentially filled device in their trial had thigh cuffs as well as calf cuffs and the single bladder system had only calf com-

pression, it is not certain that the difference in the frequency of proximal (thigh) thrombi was attributable to the sequential filling. In a subsequent study, Nicolaides et al.³⁰ compared the sequentially filled device applied for at least 3 days and followed by elastic stockings *versus* electrical calf stimulation *versus* low-dose heparin, and they found the results of external pneumatic compression and heparin to be roughly equivalent. In the system employed by Nicolaides et al., the filling pressures, rise time, duration of filling, and interval between successively filled bladders were different from the corresponding values employed in the optimized device we have studied, which is not duplicated by any commercial unit now available.

Despite the improved hemodynamic effectiveness of the graded compression sequentially filled system and the superior biologic effects reflected by enhanced fibrinolytic activity, we were unable to show greater antithrombotic effectiveness for this device. There were no significant differences in the frequency of venous thrombosis in the three patient groups. Two possible explanations are: (1) regardless of the difference in hemodynamic effects, the difference in antithrombotic effectiveness among the three modes of external pneumatic compression is negligible, and the uniform compression system accomplishes all that can be expected of external pneumatic compression in respect to prevention of venous thrombosis, or (2) a real difference exists, with graded sequential compression being superior to uniform compression, but because of the limited number of patients or for other reasons, the study was insufficient in statistical power to show the difference (*i.e.*, there is a possibility of a beta error).³¹ Even if the latter is true, however, the difference in efficacy of the three forms of

calf compression is probably not large, and one must question whether the increment in clinical benefit would be worth the additional cost and complexity of engineering and producing the graded sequential filling system.

It remains possible that, in a population at even higher risk than the neurosurgical patients (such as those with reconstructive operations on the hip), a hemodynamically superior system applying graded pressure with sequential filling might have demonstrably better antithrombotic efficacy than systems in which fluid mechanical features are not optimized.

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References

- Simon TL, Stengle JM. Antithrombotic practice in orthopaedic surgery. *Clin Orthop* 1974; 102:181-187.
- Morris GK. Prevention of venous thromboembolism. A survey of methods used by orthopaedic and general surgeons. *Lancet* 1980; 572-574.
- Conti S, Daschbach M. Venous thromboembolism prophylaxis. *Arch Surg* 1982; 117:1036-1040.
- Skillman JJ, Collins REC, Coe NP, et al. Prevention of deep vein thrombosis in neurological patients: a controlled, randomized trial of external pneumatic compression boots. *Surgery* 1978; 83(3):354-358.
- Turpie AGG, Gallus AS, Beattie WS, Hirsh J. Prevention of venous thrombosis in patients with intracranial disease by intermittent pneumatic compression of the calf. *Neurology* 1977; 27(5):435-438.
- 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.
- Coe NP, Collins REC, Klein LA, et al. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic boots. *Surgery* 1978; 83:230.
- Salzman EW, Ploetz J, Bettman M, et al. Intraoperative external pneumatic calf compression to afford long-term prophylaxis against deep vein thrombosis in urological patients. *Surgery* 1980; 87(3):239-242.
- Hills NH, Pflug JJ, Jeyasingh K, et al. Prevention of deep-vein thrombosis by intermittent pneumatic compression of calf. *Br Med J* 1972; 1:131.
- Roberts VC, Cotton LT. Prevention of postoperative deep vein thrombosis in patients with malignant disease. *Br Med J* 1974; 1:358.
- Clarke-Pearson DL, Synan IS, Hinshaw WM, et al. Prevention of venous thromboembolism by external pneumatic calf compression in patients with gynecologic malignancy. *Obstet Gynecol* 1984; 63:92-98.
- Harris WH, Athanasoulis CA, Waltman AC, Salzman EW. Prophylaxis of deep-vein thrombosis after total hip replacement. *J Bone Joint Surg* 1985; 67-A(1):57-62.
- Hull R, Delmore TJ, Hirsh J, et al. Effectiveness of intermittent pulsatile elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. *Thromb Res* 1979; 16:37-45.
- Salzman EW, Sobel M, Lewis J, et al. Prevention of venous thromboembolism in unstable angina pectoris. *N Engl J Med* 1982; 306:991.
- Knight MTN, Dawson R. Effect of intermittent compression of the arms on deep venous thrombosis in the legs. *Lancet* 1976; 2:1265.
- Olson DA, Kamm RD, Shapiro AH. Bioengineering studies of periodic external compression as prophylaxis against deep vein thrombosis. Part II: experimental studies on a simulated leg. *ASME, J Biomech Eng* 1982; 104.
- Kamm R, Butcher R, Froelich J, et al. Optimization of parameters of external pneumatic compression for prophylaxis against deep vein thrombosis: radionuclide gated imaging studies. *Cardiovasc Res* 1986; 20:588-596.
- Flanc C, Kakkar VV, Clarke MB. The detection of venous thrombosis of the legs using 125I-labelled fibrinogen. *Br J Surg* 1968; 55(10):742-747.
- Wheeler HB, Pearson D, O'Connell D, et al. Impedance phlebography. Technique, interpretation and results. *Arch Surg* 1972; 104:164.
- Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis of the leg. *Arch Surg* 1972; 104:134.
- Coppe D, Wessinger SJ, Ransil BJ, et al. Sex differences in the platelet response to aspirin. *Thromb Res* 1981; 23:1-21.
- Moroz LA. Increased blood fibrinolytic activity after aspirin ingestion. *N Engl J Med* 1977; 296(10):525-529.
- Mansfield AO. Alteration in fibrinolysis associated with surgery and venous thrombosis. *Br J Surg* 1972; 59:754.
- Knight MTN, Dawson R, Melrose DG. Fibrinolytic response to surgery. Labile and stable patients and their relevance to postoperative deep vein thrombosis. *Lancet* 1977; 2:370.
- Bulpitt CJ. Confidence intervals. *Lancet* 1987; 1:494-497.
- Fleiss JL. *Statistical Methods for Rates and Proportions*. New York: J. Wiley & Sons, 1973; 23-33.
- Comp PC, Jacocks RM, Taylor FB. The dilute whole blood clot lysis assay: a screening method for identifying postoperative patients with a high incidence of deep venous thrombosis. *J Lab Clin Med* 1979; 93(1):120-127.
- Clayton JK, Anderson JA, McNicol GP. Preoperative prediction of postoperative deep vein thrombosis. *Br J Med* 1976; 2:910-912.
- Nicolaides AN, Fernandes JF, Pollock AV. Intermittent sequential pneumatic compression of the legs in the prevention of venous stasis and postoperative deep venous thrombosis. *Surgery* 1980; 87(1):69-76.
- Nicolaides AN, Miles C, Hoare M, et al. Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery* 1983; 94:21-25.
- Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *New Engl J Med* 1978; 299(13):690-694.