Efficacy of mechanical prophylaxis for venous thromboembolism in patients with brain tumors

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Patients with brain tumors are at considerable risk for the formation of venous thromboemboli. One method of preventing these complications is mechanical prophylaxis in which an external pneumatic compression device and graduated elastic compression stockings are used. Evidence indicates that these devices prevent deep venous thrombosis (DVT) and pulmonary embolism (PE) by limiting venous stasis and increasing fibrinolytic activity at both the local and systemic levels. The authors present evidence for the occurrence of both mechanisms and discuss the use of mechanical compression in the setting of surgery for brain tumors. They also present data proving the efficacy of these devices in patients who undergo craniotomy with motor mapping for resection of glioma and in whom the contralateral leg receives no prophylaxis. Finally, they comment on the use of anticoagulation therapy both in addition to and in place of mechanical prophylaxis.

KEY WORDS • venous thromboembolism • external pneumatic compression device • compression stocking • craniotomy • motor mapping • glioma

The incidence of DVT in neurosurgical patients ranges between 2 and 50%.^{1,5,10,12,19,23,27,40,47,48,51,53} The rate of DVT and PE is thus quite significant and can lead to fatal outcomes. Neurosurgical procedures entail a 1.5 to 5% risk of PE and a 9 to 50% rate of mortality from this disorder.²³ The prevention of VTE in neurosurgery by using mechanical prophylaxis is well established. Current modalities for mechanical prophylaxis involve pneumatic compression devices, graduated elastic compression stockings, or a combination of both. Prevention of VTE by using mechanical devices addresses tenets of the Virchow⁵⁴ triad: endothelial damage, venous stasis, and hypercoagulability. Mechanical prophylaxis appears to prevent thromboembolic complications by limiting venous stasis and diminishing hypercoagulability.

We provide a brief overview of the pathogenesis of thrombosis in patients undergoing neurosurgery and discuss the rationale for mechanical prophylaxis in the prevention of VTE. We also address a variation on mechanical prophylaxis in patients undergoing craniotomy with motor mapping. Finally, we comment briefly on the supplementation of mechanical prophylaxis with anticoagulation therapy.

Hypercoagulability in the Postoperative Patient

Neurosurgical patients are at considerable risk of ex-

periencing thromboembolic complications. Neurological deficits caused either by the disease process or the procedures designed to treat it may limit patient activity and promote venous stasis in immobile extremities. Craniotomies performed for resection of malignant tumors have been proven to present an increased risk of VTE,^{8,51,53} especially when the diagnosis is glioma.^{7,15,35,44} Malignancy alone has proven to be a significant risk factor for DVT and PE.^{18,28} Procedures for brain tumor resection are often time-consuming, and lengthy operations lead to prolonged venous stasis.⁴⁸ The thromboembolic risks associated with neurosurgery cannot be ignored either in the operating room or during recovery.

The postoperative period is one marked by significant alterations in clotting enzymes. Patients undergoing surgical procedures have been noted to have increased inhibition of tPA, a potent clot-dissolving enzyme that converts plasminogen to plasmin (Fig. 1).^{28,32} Diminished tPA function will result in a reduced capacity for clearance of thrombi. Owen, et al.,³⁹ documented a marked imbalance between the proteolytic enzymes thrombin and plasmin in patients who underwent craniotomy. When this imbalance was allowed to persist, thrombi developed with increased frequency in these patients.

Localized hypoxemia within venous channels may further promote clot formation in the perioperative period. Hamer, et al.,²² demonstrated that the valve pockets of veins become readily hypoxic during nonpulsatile flow. They demonstrated that diminished flow promoted early thrombus formation on the hypoxic valve cusps in as little as 2 hours. Lengthy neurosurgical procedures and the pro-

Abbreviations used in this paper: DVT = deep venous thrombosis; PE = pulmonary embolism; tPA = tissue plasminogen activator; VTE = venous thromboembolism.

Fig. 1. Schematic diagram of the clotting cascade showing endothelial injury through both the intrinsic and extrinsic pathways. Mechanical prophylaxis has been shown to normalize the thrombin/plasmin ratio (black arrows), increase tPA levels, and decrease levels of plasminogen activator inhibitor (PAI; white arrows). Alterations in the levels of these proteolytic enzymes have been implicated in the reduced incidence of thromboembolism formation. Roman numerals denote clotting factors. PI = pathway inhibitor; TF = tissue factor.

longed inactivity associated with them are likely to reproduce these hypoxic conditions and predispose patients to clot formation.

Pneumatic Compression Devices

External pneumatic compression devices have been shown to prevent the formation of DVTs in neurosurgical patients.^{47,50,51} Modern devices evacuate blood from lower-extremity vessels in an automated fashion. In brief, a microprocessor directs pressurized air (for example, at 45 mm Hg) into segmental diaphragms secured around the leg for a fixed period of time (for example, for 11 seconds).³⁰ The compression is delivered in a sequential manner up the leg, producing a wavelike milking effect to evacuate leg veins. Sequential devices have been proven to be more effective than single-chamber, evenly distributed pressure in preventing DVTs.³⁷ The compression is set to cycle regularly (for example, every 60 seconds). Devices are available for feet, calves, and/or thighs. Published contraindications for the use of these devices are listed in Table 1.

Pneumatic compression may exert its protective effect against thrombus formation in part by limiting venous stasis. Calnan, et al.,¹¹ were one of the first groups to illustrate that intermittent, rhythmic compression of the lower ex-

TABLE 1

*Contraindications for the use of sequential pneumatic compression devices**

dermatitis
postop vein ligation
gangrene
recent skin graft
severe ischemic vascular disease
severe lower-extremity edema
extreme leg deformity
suspected preexisting DVT

* According to Jeffery and Nicolaidis.

tremity mimics the normal pumping of calf muscles. Soon after, Sabri, et al.,⁴² demonstrated a 400% increase in femoral vein pulsatility and a 250% increase in peak femoral venous blood flow when the devices were applied to the lower limbs of greyhound dogs. Comparable results were found in the lower extremities of humans who received pneumatic compression.⁴¹ In more modern studies investigators have shown increased blood flow velocities in the popliteal and common femoral veins by applying intermittent pneumatic compression to the foot alone.³¹ Mittelman, et al.,³⁶ compared the use of calf and thigh compression with calf compression alone and found an enhanced effect of blood clearance with sequential compressions of the calf and thigh. Similarly, Delis, et al.,¹⁶ found greater outflow during foot plus calf compression when comparing it with foot compression alone. Current prophylactic devices most frequently compress at least two regions of the lower extremity, although more limited devices have retained some popularity.

Mechanical compression devices appear to exert part of their prophylactic effect through enhanced fibrinolysis.^{14,25,49} Early studies in which euglobulin clotting times were analyzed as a marker for systemic fibrinolysis activity in postoperative patients demonstrated that calf compression augments clot breakdown.^{3,33,43} Weitz, et al.,⁵⁵ showed that intermittent pneumatic calf compression, by preserving the normal thrombin/plasmin ratio in blood samples obtained in patients who receive this therapy when compared with those not receiving pneumatic compression, averts the hypercoagulable state noted by Owen, et al.³⁹ Intermittent pneumatic compression has been shown to increase the amount of tPA release and to decrease levels of plasminogen activator inhibitor.²⁵ This benefit may be short-lived, however; diminished fibrinolytic activity is seen from several minutes²⁵ to 18 hours³³ after discontinuation of pneumatic compression.

Various permutations of both upper- and lower-extremity compression have been tested to increase blood clearance and ultimately prevent VTEs. Nearly 30 years ago, Knight and Dawson³³ conducted a study in which they applied intermittent compression to the upper extremities of patients who had undergone surgery, and noted a reduced incidence of DVTs in the legs and increased serum fibrinolytic activity. Tarnay, et al.,⁴⁹ also showed increased fibrinolysis in patients receiving compression in the arms, although this difference was not statistically significant. Another interesting finding of this study was the increased fibrinolysis detected in serum samples obtained in the pa-

tient's arm after administration of pneumatic compression to the legs. This effect appeared to be proportional to the volume of tissue compressed; increased fibrinolysis was detected in patients who wore long compression boots when compared with those given shorter boots. The results of these studies indicate that the fibrinolytic activity promoted by mechanical prophylaxis has both local and systemic effects in protecting against clot formation.

Compression Stockings

An alternative or additional means of preventing thromboembolic complications is the graduated elastic compression stocking.^{2,24,26,45} These devices apply continuous circumferential pressure to the lower extremity in a graduated fashion (~18 mm Hg at the ankle to ~8 mm Hg at the thigh)⁴⁶ as a means of increasing venous clearance and preventing venous stasis. The stockings are contoured to the lower extremity to prevent tenting and focal constriction. Similar care should be exercised in selecting patients to receive stockings as is taken in choosing patients for treatment with pneumatic devices. The contraindications listed in Table 1 can be applied for stocking use as well.

In most neurosurgical practices, compression stockings are combined with pneumatic devices as a standard of care, presumably to enhance the prophylactic benefit of each. To test the theory that the protective effect of these devices is additive, Keith, et al.,²⁹ used Doppler ultrasonography imaging to measure the peak venous velocities produced in superficial femoral veins by the individual and simultaneous use of graduated compression stockings and intermittent pneumatic compression boots. Although their study was not designed to consider the effect on thrombosis formation, blood flow velocity served as a surrogate measure for the limited stasis and venous evacuation that could ultimately lead to the formation of thromboses. The results showed no synergistic effect on venous outflow when these devices were used simultaneously.

Two separate groups performed direct comparisons between compression stockings and pneumatic devices to assess the effectiveness of these modalities in reducing the risk of venous thrombosis.^{9,52} Based on their results, stockings appear to be as effective in VTE prevention as pneumatic compression devices, and stockings have the added benefit of lower cost. Patients also suffer less discomfort with stockings when compared with the pressure associated with intermittent leg compressions from pneumatic devices. In addition, the garments do not require assembly once fitted, are not subject to malfunction or troubleshooting, and facilitate patient mobility and ambulation during the postoperative recovery period.

Despite these findings, the combined approach in which both stockings and pneumatic devices are used remains popular, likely because of their relative ease of application or simply out of habit. Cost-conscious healthcare may limit their combined use in the future. In the meantime, practitioners should not be overly concerned when discomfort leads to discontinuation of pneumatic compression; these patients are not at any proven risk as long as they continue to use their compression stockings.

Prophylaxis After Craniotomy for Motor Mapping

Patients with lesions involving crucial speech or motor

cortex present an added challenge in the prevention of VTE. Preservation of vital cortical structures necessitates intraoperative motor mapping and exposure of the contralateral lower extremity to monitor response to stimulation. The question then becomes: does craniotomy for motor mapping predispose neurosurgical patients to VTE formation?

To test this theory, we conducted a retrospective review of 188 patients who underwent craniotomy and motor mapping for glioma.⁴ In prior studies in which the use of mechanical prophylaxis for VTE was investigated, compression devices and stockings were routinely placed on both lower extremities. Given the scarcity of published data for unilateral prophylaxis, all patients included in this study received external pneumatic compression devices and compression stockings on the lower extremity ipsilateral to the side of the brain tumor and motor mapping. Patients with prior or current VTEs were excluded.

Our analysis indicated that motor mapping without contralateral mechanical prophylaxis does not place patients at a higher risk for VTE. We reported a 2.2% incidence of DVT and a 1.1% incidence of PE, which were comparable to statistics reported for neurosurgical patients receiving standard mechanical prophylaxis. A comprehensive review of this series showed no statistical significance for patient age, duration of surgery, or preoperative values for prothrombin and partial thromboplastin times (Table 2).

Supplementary Anticoagulation Therapy

The use of anticoagulation therapy during the perioperative period has been limited by concerns about intracranial bleeding.^{13,17} In a recent survey conducted among neurosurgeons, as many as 29% of respondents associated low-molecular-weight heparin with bleeding complications.²⁰ Added to this is the proven efficacy and safety of mechanical prophylaxis when compared directly with low-dose subcutaneously administered heparin.^{37,38} Nevertheless, the use of perioperative anticoagulation therapy continues to have support and its safety in neurosurgical patients has been proven.^{1,6,12,21,34} A summary of these regimens is provided in Table 3.

The most reasonable solution for treatment concerns would be to tailor each prophylactic regimen to the individual. Patients with a higher than average thromboembolic risk warrant more aggressive prophylaxis. If the contraindications listed in Table 1 preclude the use of mechanical prophylaxis, anticoagulation therapy may be an appropriate supplementary or alternative treatment.

CONCLUSIONS

Mechanical prophylaxis for thromboemboli is an integral part of modern neurosurgical practice. It remains an effective means of preventing DVT and PE, both intra- and postoperatively. Compression stockings and pneumatic devices are relatively equivalent in their prevention of VTE. Their effectiveness is not diminished when one leg is not treated with compression during motor mapping. Concomitant anticoagulation therapy during the postoperative period appears not only to be safe but also to protect patients further against thromboembolic complications.

TABLE 2

*Demographic data in patients at UCSF who underwent craniotomy with motor mapping for glioma**

Factor	Total No. w/ DVT/PE	No. w/o DVT
no. of patients	21	173
sex		
male	11	102
female	10	71
resection		
primary	12	96
revision	9	77
mapping		
motor	21	166
motor & speech	0	7
side of op		
rt	12	118
lt	9	55
habits		
smoking	4	44
alcohol	0	26
IV drug use	0	1
CV risk factors		
CV disease	6	32
HTN	4	25
valve disease	2	0
high lipid levels	0	3
high cholesterol	0	11
previous op	16	149
intracranial	11	102
extracranial	5	47
anticoagulant drugs on admit	0	coumadin, 2; LMW heparin, 2; aspirin, 3; other NSAIDs, 2
mean duration of op	6.8 hrs	6.9 hrs
intraop DVT prophylaxis		
SCD	19	0
PCD	0	153
stockings	21	160
side specified	7	93
side not specified	14	80
dx		
DVT	20	NA
PE	7	NA
method of DVT dx		
US	5	NA
H & P	1	NA
unknown	15	NA
method of PE dx		
helical CT	2	NA
presumed hypoxemia + DVT	1	NA
unknown	14	NA
side of DVT		
w/o prophylaxis only	7	NA
w/ prophylaxis only	2	NA
both sides w/ prophylaxis	1	NA
bilat DVTs	4	NA
prophylaxis unspecified but DVT contralat to op side	3	NA
DVT side unstated	2	NA
follow-up time (mos)†		
mean	11.7	13.5
median	9.0	9.0
other risk factors		nephrotic syndrome + vasculitis, 1; OCPs, 2; recent trauma, 4

* Portions of these data were previously analyzed and included in a prior publication (Auguste, et al.). Abbreviations: CT = computerized tomography; CV = cardiovascular; dx = diagnosis; H & P = history and physical examination; HTN = hypertension; IV = intravenous; LMW = low-molecular-weight; NA = not applicable; NSAID = nonsteroidal antiinflammatory drug; OCP = oral contraceptive pill; PCD = pneumatic compression device; SCD = sequential compression device; UCSF = University of California, San Francisco; US = ultrasound.

† Follow up for all patients: less than 3 months, 24%; 3 to 6 months, 12.4%; 6 to 9 months, 13.8%; 9 to 12 months, 9.5%; 1 to 2 years, 20.4%; 2 to 3 years, 13.9%; 3 to 4 years, 4.4%; more than 4 years, 1.4%.

TABLE 3

*Literature review of evidence-based regimens for safe anticoagulation therapy in patients undergoing neurosurgery**

Authors & Year	Anticoagulating Agent	Regimen
Cerrato, et al., 1978	heparin	5000 U Q 8 hrs
Bostrom, et al., 1986	heparin	5000 U Q 12 hrs
Agnelli, et al., 1998	enoxaparin	40 mg QD
Macdonald, et al., 1999	heparin	5000 U Q 12 hrs & 5000 U Q 8 hrs
Goldhaber, et al., 2002	enoxaparin	40 mg QD

* QD = every day.

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