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ORIGINAL ARTICLE

Randomized controlled trial of a new portable calf compression device (Venowave) for prevention of venous thrombosis in high-risk neurosurgical patients

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Summary. *Background:* Patients undergoing neurosurgical procedures are at risk of venous thromboembolism (VTE), but often have contraindications for anticoagulant prophylaxis. *Objectives:* To assess the efficacy and tolerability of a new, lightweight, portable, battery-powered, intermittent calf compression device, Venowave, for the prevention of VTE in neurosurgical inpatients. *Patients/Methods:* We performed an open randomized controlled trial comparing Venowave with control for the prevention of VTE in patients undergoing neurosurgery. The primary outcome was the composite of asymptomatic deep vein thrombosis (DVT) detected by screening venography or compression ultrasound performed on day 9 (± 2 days) and symptomatic VTE. *Results:* We randomized 75 patients to receive Venowave devices and 75 to the control group. All patients were prescribed graduated compression stockings and physiotherapy. VTE occurred in three patients randomized to Venowave and in 14 patients randomized to control (4.0% vs. 18.7%, relative risk 0.21; 95% confidence interval 0.05–0.75, $P = 0.008$). Similar reductions were seen for proximal DVT (2.7% vs. 8.0%) and symptomatic VTE (0% vs. 2.7%), and the results were consistent in all subgroups examined. *Conclusions:* Venowave devices are effective in preventing VTE in high-risk neurosurgical patients.

Keywords: deep vein thrombosis, mechanical prophylaxis, neurosurgery, pulmonary embolism, venous thromboembolism, Venowave.

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Introduction

Patients undergoing neurosurgical procedures are at high risk of venous thromboembolism (VTE). In patients not receiving thromboprophylaxis, the reported frequency of any VTE (symptomatic and asymptomatic) has ranged from 29% to 60% [1–3], symptomatic VTE has occurred in as many as 7%, and fatal pulmonary embolism (PE) has occurred in 0.5% [2]. Anticoagulants are effective for the prevention of VTE, but are often not used in neurosurgical patients, because of concerns about the risk of bleeding, which can be associated with devastating sequelae [4–7]. Graduated compression stockings (GCSs) and mechanical compression devices are attractive as alternatives to anticoagulants, because they are effective for the prevention of VTE and do not increase the risk of bleeding [8–10]. However, existing mechanical methods have limitations. GCSs are often not correctly fitted, and compliance is poor [11,12]. Mechanical compression devices are uncomfortable for patients [11,13–17], and most of the currently available intermittent mechanical compression devices rely on an external power source, which restricts patient mobility.

Venowave is a novel, portable, battery-powered calf compression device that is potentially suited for inpatient and outpatient deep vein thrombosis (DVT) prophylaxis. It is simple to use, and can be worn when the patient is moving. In this single-center, randomized, open-label study, we examined the efficacy and safety of Venowave in comparison with control on a background of standard VTE prophylaxis for the prevention of venous thrombosis in high-risk neurosurgical patients. The primary outcome was the composite of asymptomatic DVT detected by screening venography or compression ultrasound performed at day 9 (± 2 days) and symptomatic VTE.

Methods

The study was performed at the Hamilton General Hospital in Hamilton, Canada. The protocol was approved by the local Institutional Ethics Review Board, and all patients provided

written informed consent. The protocol was registered at Australian New Zealand Clinical Trials Registry, ACTR number 12611000424909.

Study patients

Neurosurgical patients aged 18 years or older admitted to Hamilton General Hospital for cranial or spinal neurosurgery were eligible for enrollment in the study. Additionally, neurosurgical patients admitted with intracranial hemorrhage (subarachnoid, intracerebral, or subdural) who had motor deficits but were not undergoing surgery were eligible if consent was obtained within 24 h of hospital admission.

Patients were excluded if they had contraindications to the use of mechanical compression devices, including leg ulceration, symptomatic peripheral neuropathy, or peripheral arterial disease. Patients who could not undergo venography because of allergy to contrast medium or pre-existing renal impairment (defined as a glomerular filtration rate of < 50 mL min^{-1}) were also excluded.

Venowave calf compression device

Venowave (Saringer Research Incorporated, Stouffville, Canada) is a compact, battery-powered, portable calf compression device (Fig. 1). It consists of a rotating gear-motor attached to a flexible sheet via a linkage that generates a repetitive waveform motion with a frequency of six cycles per minute. It has been shown to increase peak venous flow in the common femoral and popliteal veins in normal subjects and in patients with postphlebitic syndrome [18]. Venowave has been evaluated in the setting of severe postphlebitic syndrome, and found to be effective and well tolerated [19]. The device has been approved by the Food and Drug Administration and Health Canada for the prevention of VTE, but has not been previously evaluated for this indication.

Study design and interventions

Eligible consenting patients were randomly allocated to application of Venowave or to the control group (no Venowave). Patients were randomized by use of a computer-generated randomization sequence concealed in sequentially numbered, opaque, sealed envelopes prepared by a statistician not otherwise involved in the study. Surgical patients were randomized in the postoperative recovery room. Non-surgical patients were randomized immediately prior to study entry. Patients and care providers were aware of treatment allocation, because the Venowave devices could not be effectively concealed.

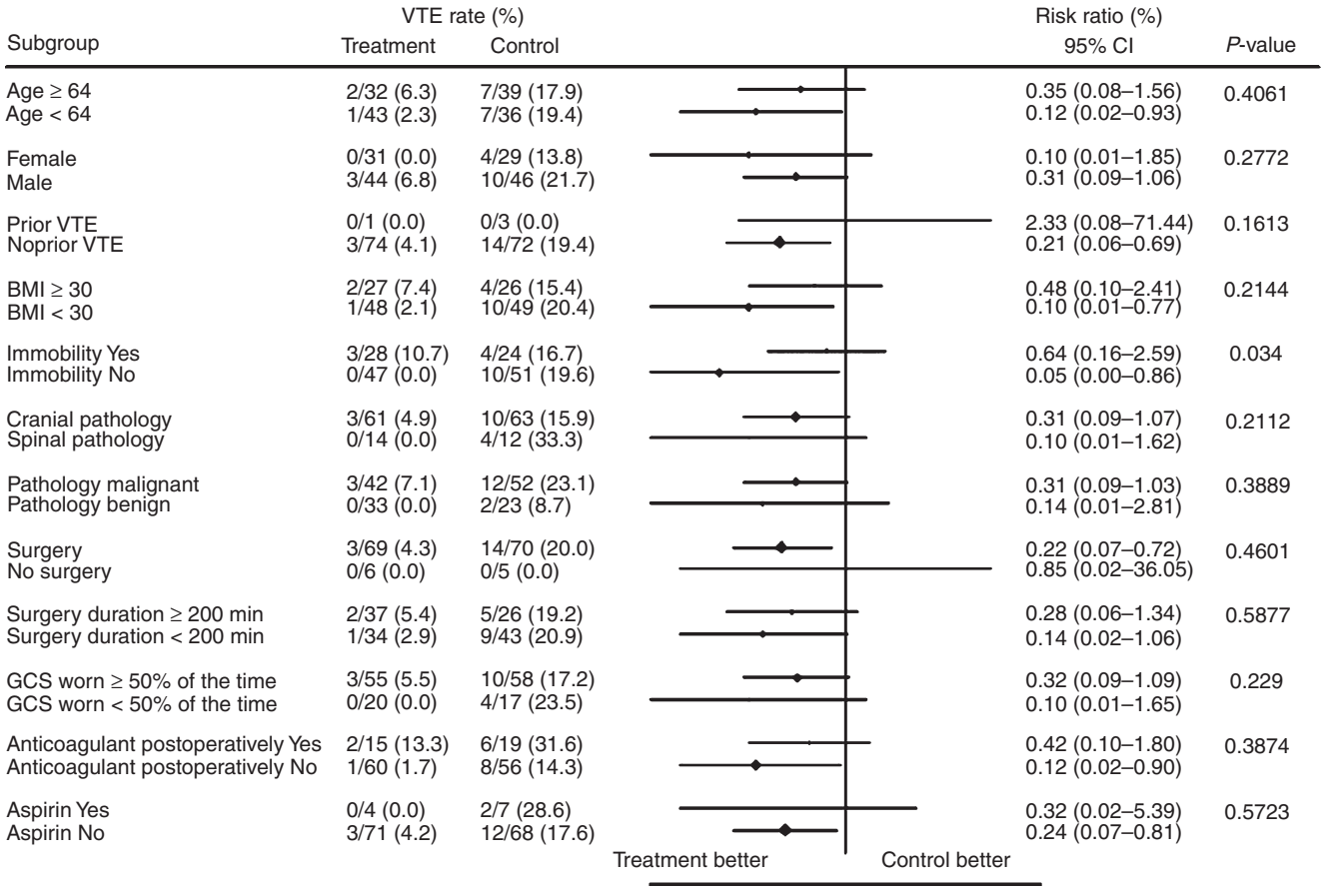

Fig. 1. Relative risk of venous thromboembolism (VTE) in Venowave versus control groups according to subgroups.

All patients received other VTE prophylaxis according to usual care as determined by the surgeon responsible for the patient's care. As part of the neurosurgical unit protocol, all patients were prescribed below-knee GCS and underwent early mobilization. Patients could also receive pharmacologic prophylaxis (aspirin, unfractionated heparin, or low molecular weight heparin [LMWH]) at the discretion of the neurosurgeon.

In patients randomized to the Venowave group, Venowave devices were applied to both calves within 4 h of surgery or within 24 h of admission to hospital in non-operated patients. Venowave devices were worn continuously (removed for showering only), and their use was continued until the development of symptomatic VTE, patient refusal, or venographic or ultrasound examination. Patients who were not willing to wear the devices continuously were encouraged to wear the devices for the maximum tolerated number of hours daily. The use of Venowave devices in hospital was monitored at least twice daily (including weekends), and compliance was recorded. Patients discharged before day 7 who were willing to return for outpatient venography received home visits at least daily by the study nurse or doctor to optimize compliance with the Venowave devices. Compliance with GCS use was also recorded.

Patient satisfaction with Venowave was assessed with a previously validated patient questionnaire completed by each patient at study completion. Patients were asked to grade their comfort when wearing Venowave during the day and during the night (visual scale of 0–6, where 0 is very uncomfortable and 6 is very comfortable), and were asked whether they experienced pruritis or sweating, whether the devices interfered with mobility or physiotherapy, and whether the devices interfered with sleep (all symptoms were graded as mild, moderate, or severe). Patients were also asked whether they would use Venowave for VTE prophylaxis in the future, and were encouraged to comment on their experience with the devices.

In addition, a standardized data sheet completed daily by the study nurse recorded data on device slippage and impact on mobility, skin integrity, and patients' ability to self-manage the devices (apply, adjust, battery change).

Patient compliance with Venowave was assessed with a compliance chart completed 8-hourly by the ward or study nurse. After discharge from hospital, the patient or carer kept a daily log, which was reviewed by the study nurse at least daily. We categorized the pattern of device use as 'continuous' when the patient used the device for ≥ 23 h per day throughout the study period, 'intermittent' when the patient used the device every day of the study but for < 23 h per day, and 'discontinued' if the patient stopped using the device before scheduled venography.

Outcome measures

The primary efficacy outcome of all VTEs was a composite of all asymptomatic DVTs (detected by screening venography or compression ultrasound), symptomatic DVT (objectively confirmed by compression ultrasound), and symptomatic PE confirmed by computed tomography pulmonary angiography (CTPA).

Patients with clinically suspected DVT underwent compression ultrasound. If ultrasound examination findings were negative, the patient continued in the study until the scheduled screening venography. Patients with clinical features suggestive of PE underwent CTPA. Patients with a normal CTPA finding continued until their scheduled screening venography.

All patients were scheduled to undergo a screening bilateral venogram at day 9 ($\pm$ 2 days) after study enrollment or at discharge if they were discharged from hospital earlier and were unable to return for an outpatient venogram. DVT was defined as a constant intraluminal filling defect in a deep leg vein that was seen on two or more views. Venograms were performed by one of two experienced interventional radiologists who were unaware of patient treatment allocation. Patients who were unable to undergo a venogram (a medical contraindication such as emergent renal dysfunction, acute medical illness precluding the procedure, failed leg vein cannulation, or patient refusal) underwent bilateral full-length compression ultrasound. The radiographer performing compressive ultrasonography was blinded to patient treatment allocation. A radiologist who was not aware of patient study allocation verified all positive ultrasound findings. Venograms were independently adjudicated at study completion by an expert reader who was blinded to the clinical data and patient treatment allocation.

Statistical analysis

The calculation of sample size was based on an expected incidence of VTE of 40% in the control group and of 15% in the Venowave group. Approximately 150 patients would be needed to detect a 60% difference with an alpha level of 0.05 (two-tailed) and a beta level of 0.20, assuming that venographic endpoint assessment would be available for 80% of the enrolled patients.

The efficacy analysis compared the combined rates of symptomatic, objectively confirmed VTE, or DVT detected by screening venography or ultrasound, in patients randomized to Venowave and to no devices. The rates of venous thromboembolic events in the two groups were compared by use of Fisher's exact test. The *P*-values were two-sided, and values < 0.05 were considered significant.

Results

Between May 2009 and November 2010, 150 patients were randomly assigned to Venowave application or to the control group. The groups were well balanced with respect to demographic characteristics (Table 1) and the distribution of neurosurgical diagnoses and procedures (Table 2). The use of GCSs was similar in the two groups, but more patients randomized to the control group received postoperative prophylaxis with an anticoagulant or aspirin (34.7% vs. 25.3%) (Table 3).

Table 1 Baseline characteristics

	Control group (n = 75)	Venowave group (n = 75)
Age (years)		
Mean (SD)	62.11 (11.82)	61.97 (10.11)
Median	64	62
Min.–max.	29–86	38–87
Sex		
Female (%)	29 (38.7)	31 (41.3)
Male (%)	46 (61.3)	44 (58.7)
Prior history of VTE (%)	3 (4)	1 (1.3)
BMI		
Mean (SD)	28.33 (8.08)	27.71 (5.43)
BMI > 30 (%)	26 (34.7)	25 (33.3)
Immobility* (%)	24 (32)	28 (37.3)
Paralysis (%)	11 (14.7)	19 (25.3)

BMI, body mass index; SD, standard deviation; VTE, venous thromboembolism. *Immobility defined as chair-bound or bed-bound, and unable to move without assistance to the bathroom.

Table 2 Distribution of neurosurgical diagnoses and procedures

	Control group (n = 75)	Venowave group (n = 75)
Cranial pathology (%)	63 (84.0)	61 (81.3)
Glioma	17	13
Meningioma	9	8
Carcinoma metastasis	19	19
ICH	4	4
Subdural bleed	4	5
Other	10	12
Spinal pathology (%)	12 (16.0)	14 (18.7)
Tumor	5	3
Stenosis	6	11
Other	1	0
Site of surgery		
Intracranial surgery (%)	58 (77.3)	55 (73.3)
Craniotomy	53	47
Burr holes	3	3
Other	2	5
Spinal surgery (%)	12 (16)	14 (18.7)
No surgery (%)	5 (6.7)	6 (8.0)
Surgery duration (min)		
Mean (SD)	201 (121.4)	214 (97.9)
Median	171	201
Min.–max.	39–707	45–597

ICH, intracerebral hemorrhage; SD, standard deviation.

Table 3 Use of venous thromboembolism prophylactic co-interventions postoperatively

Co-intervention	Control group, n = 75 (%)	Venowave group, n = 75 (%)
GCS prescribed	75 (100)	75 (100)
GCS worn ≥ 50% of the time	59 (78.7)	54 (72.0)
Anticoagulant*	19 (25.3)	15 (20)
Aspirin	7 (9.3)	4 (5.3)

GCS, graduated compression stocking. *Any unfractionated heparin or low molecular weight heparin given in the postoperative period.

Of the 150 study patients, 142 (94.7%) underwent screening venography and/or compression ultrasonography that was adequate for the final analysis. Four patients in the Venowave group and four patients in the control group did not undergo screening for DVT, and no patient was lost to follow-up (Table 4). The mean time to screening was similar for the two groups: 7.3 days (standard deviation [SD] 2.1) in the Venowave group, and 7.5 days (SD 2.1) in the control group.

VTE

For patients in the Venowave group, the rate of VTE was 4.0%, as compared with 18.7% in the control group (P = 0.008) (Table 5). The relative risk of VTE with Venowave use as compared with no Venowave use was 0.21 (95% confidence interval 0.05–0.75). The respective rates of proximal DVT were 2.7% vs. 8.0% (P = 0.28) and those of symptomatic VTE were 0% vs. 2.7% (P = 0.5) in patients randomized to Venowave and controls, respectively. No cases of PE occurred during the study period. Results were consistent in all major subgroups examined, with the exception of the presence of immobility, which showed a nominally significant interaction with treatment (Fig. 2).

Table 4 Use of venography and ultrasonography to assess outcome

Category	Control group	Venowave group
Randomized	75	75
Venographic study available (%)	53 (70.7)	49 (65.3)
Ultrasonographic study available (%)	12 (16)	16 (21.3)
Reasons for ultrasonography		
Medical contraindication to venography	5	4
Failed leg cannulation	4	6
Patient refusal	2	5
Other	1	1
Both (one leg venogram, one leg ultrasound) (%)	6 (8)	6 (8)
None (%)	4 (5.3)	4 (5.3)
Patient refusal	3	3
Other	1	1

Table 5 Rates of venous thromboembolism in patients randomized to the control and Venowave groups

Event	Control group, N = 75 (%)	Venowave group, N = 75 (%)	P-value	Relative risk (95% CI)
DVT	14 (18.7)	3 (4.0)	0.008	0.21
Proximal	6 (8.0)	2 (2.7)	0.28	(0.05–0.75)
Distal	8 (10.7)	1 (1.3)	0.50	
Bilateral	5 (6.7)	2 (2.7)	0.50	
Unilateral	9 (12.0)	1 (1.3)	0.50	
Symptomatic DVT	2 (2.7)	0 (0)	0.50	–
PE	0 (0)	0 (0)	–	–

CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism.

Fig. 2. Venowave device.

Compliance with use of Venowave

Two patients allocated to the Venowave group did not wear the devices (refusal), and were considered to be non-users. Among the remaining 73 evaluable Venowave subjects, 17 (23.3%) were continuous users, 39 (53.4%) were intermittent users, and 17 (23.3%) discontinued the use of devices before the scheduled endpoint assessment. The mean duration of Venowave use among the 73 patients who wore the devices was 82.7 h (SD 42.9) over a mean of 6.6 days.

Venowave tolerability

Seventy-two subjects allocated to the Venowave arm completed the study questionnaire. Overall, Venowave devices were well tolerated, with 75.0% (54/72) of users reporting that they would use the devices for venous thrombosis prophylaxis in the future. Only 9% (7/72) of patients reported pruritis or sweating, and all graded the discomfort as mild or moderate.

Patients reported high comfort scores when using the devices during the day (while sitting or moving), with the mean comfort score for use during the day being 4.3/6 (SD 1.9). Of the Venowave subjects, 97.2% (70/72) reported that the Venowave devices did not affect their mobility or physiotherapy.

The Venowave devices were less well tolerated during the night, with the mean comfort score for night use being 3.5/6 (SD 2.2). Of the Venowave users, 61.1% (44/72) reported that the devices interfered with sleep, and 48.6% (35/72) discontinued Venowave use during the night.

Adverse events were uncommon. Two patients (2.7%) developed minor skin abrasions related to dislodgement of the padding wrap, which exposed the edge of the device's plate. Both patients continued using the devices following a brief interruption to allow healing. The wrap system was modified by the manufacturer following these incidents, and no further wrap displacement occurred during the study period.

Only 28% (20/72) of Venowave subjects were able to apply and adjust the devices and change batteries without assistance.

Discussion

Our results demonstrate that, as compared with controls (no Venowave), Venowave, on a background of usual thromboprophylaxis, reduced the risk of VTE by 79% in hospitalized neurosurgical patients. Venowave was associated with consistent reductions in proximal DVT (8.0–2.7%) and symptomatic VTE (2.7–0%); these were not statistically significant, although the study was not powered for these outcomes.

Anticoagulants are effective in VTE prevention in patients undergoing neurosurgery [20–22], but surveys consistently report low acceptance of this mode of prophylaxis by neurosurgeons [4–6]. Our study confirms low anticoagulant use in neurosurgical patients, with only one in five patients receiving any postoperative anticoagulant prophylaxis and very few receiving anticoagulant prophylaxis within the first 48 h of surgery or for more than 2 days. Our results, however, indicate that the benefits of Venowave are consistent irrespective of the use of anticoagulant prophylaxis.

One of the most important advantages of Venowave is its portability, which allows early mobilization and extension of the duration of mechanical prophylaxis in high-risk patients beyond the time of hospital discharge. The median day of discharge in our study was day 4, and the majority of patients randomized to Venowave continued to successfully use the device at home until the date of the scheduled venogram. This ability to continue out-of-hospital prophylaxis with Venowave is important, because it both addresses the problem of continuing prophylaxis for at-risk patients after early hospital discharge, and provides a simple and safe method of continuing prophylaxis in patients who remain at risk for weeks after hospital discharge [2]. Venowave was well tolerated, with the majority of users reporting that they would use the devices for venous thrombosis prophylaxis in the future. Venowave performed particularly well when used during the day, with the majority of patients reporting no interference with mobility or rehabilitation. Venowave was less well tolerated when patients were in bed, with almost 50% discontinuing using the device at night. In the few studies that have specifically reported on night-use compliance with other intermittent pneumatic compression (IPC) devices, the devices were also less well tolerated at night [15].

Venowave is relatively simple to apply and adjust, but only 19% of Venowave users in our study were able to manage the devices fully independently, with the remainder relying on a

study nurse or family member to provide assistance. This shortcoming may, in part, be explained by the functional status of our study population, with 20% having paralysis, 35% being immobilized, and many having neurologic deficits.

Compliance is closely linked to, and influenced by, patient satisfaction [17]. Adverse events, including sweating, hotness, and pruritis, occurred in only 9% of Venowave users, an incidence that compares very favorably with the reported 40% incidence in patients receiving prophylaxis with other intermittent calf compression devices [13].

Intuitively, prophylaxis would be most effective if patients were exposed to the effects of the intervention for 24 h a day. However, such an objective is often not achieved with either physical or pharmacologic methods of prophylaxis. In our study, only 53.3% of patients in the Venowave arm had used the devices for > 50% of the time, but this level of usage was sufficient to prevent nearly 80% of the VTE events. This dissociation between hours of daily usage and efficacy provides clues to the pathogenesis of venous thrombosis and the mechanism of DVT prevention by increasing blood flow. There is evidence that many venous thrombi are initiated by blood pooling in the venous sinuses of the calf, which promotes thrombosis by both causing anoxic damage to adjacent endothelial cells and by allowing the products of activated blood coagulation to accumulate [23,24]. On the basis of our findings, we speculate that improved emptying of calf veins for even 12 h a day or less reduces thrombogenic risk by a combination of three processes: reduction of ischemic endothelial damage, dilution of activated clotting factors, and removal of any fibrin that forms during periods of stasis, either by improved blood flow or an increase in local fibrinolysis. The evidence of effectiveness of LMWH administered once daily and low-dose heparin administered twice daily supports the notion that prevention of venous thrombosis can be achieved when the prophylactic agent exerts its effect for only about 12 h per day.

A limitation of our study, which is common to most clinical trials in venous thrombosis prophylaxis, is that the primary measure of outcome was asymptomatic DVT detected by screening venography and screening ultrasound. Future studies using a composite outcome of symptomatic thrombosis and PE will be required to confirm the benefit of Venowave, and indeed, other intermittent compression devices, as well as novel oral anticoagulants. Such future studies will require a much larger sample size.

Conclusion

Our study shows that Venowave is effective for preventing VTE in high-risk neurosurgical patients.

Disclosure of conflict of interests

This trial was supported by a grant from the Golden Horseshoe Biosciences Network and Saringer Incorporated (Saringer supplied Venowave devices).

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