

New Technologies, Diagnostic Tools and Drugs

Evaluation of a venous-return assist device to treat severe post-thrombotic syndrome (VENOPTS)

A randomized controlled trial

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Summary

Severe post-thrombotic syndrome (PTS) is responsible for considerable disability, reduced quality of life and increased health care costs. Current therapies are limited and often ineffective. We performed a two-centre, randomized, cross-over controlled trial to evaluate *Venowave*TM, a novel lower-limb venous-return assist device, for the treatment of severe PTS. Eligible subjects were allocated to receive, in randomized order, *Venowave* for eight weeks and a control device for eight weeks. The eight-week treatment periods were separated by a four-week period when no device was used (i.e. wash-out period). The primary outcome measure was a 'clinical success' defined as: i) reported benefit from the device; and ii) moderate or greater improvement in symptoms of PTS; and iii) willingness to continue using the device. Secondary outcome measures included quality of life (QOL) as measured by VEINES-QOL questionnaire (higher scores indicate better QOL), and PTS severity as measured by

the Villalta PTS scale (higher scores indicate more severe PTS). The study was registered with ClinicalTrials.gov (NCT00182208). Thirty-two patients were enrolled. Of these, 26 (80%) were also using graduated compression stockings. Twenty-six participants completed both trial periods. Clinical success occurred in 10 (31%) participants receiving *Venowave* and four (13%) participants receiving the control device, with two (6%) participants reporting a clinical success with both devices ($P=0.11$). Mean VEINES-QOL score at the end of study period was significantly greater ($P=0.004$) for *Venowave* (52.5; SD 5.8) compared to control (50.2; SD 6.2). Mean Villalta scale score at the end of study period was significantly decreased ($P=0.004$) for *Venowave* (12.2; SD 6.3) compared to control (15.0; SD 6.1). In conclusion, *Venowave* appears to be a very promising new therapy for patients with severe PTS, which may be used alone or in combination with graduated compression stockings.

Keywords

Venous thrombosis, clinical studies, deep vein thrombosis

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Introduction

Post-thrombotic syndrome (PTS) is the most frequent chronic complication of deep vein thrombosis (DVT) of the leg (1, 2). Characterised by pain and swelling, it is responsible for considerable personal disability, reduced quality of life and substantial health care costs (estimated at US \$250 million per year in North America) (3–8). Management of severe PTS presents a particu-

lar challenge to clinicians (5). The cornerstone of therapy is graduated compression stockings which have considerable clinical limitations, in that patients frequently experience only partial or no symptom relief from stockings (5, 9–11). Although pneumatic compression pumps can provide symptomatic relief for patients with severe PTS, their use is often impractical as patients must remain stationary for two hours or more per day, and the expense of the pumps is often prohibitive (12).

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Figure 1: Venowave device. Unit size (without wraps) is 9 cm x 19 cm x 4 cm. The unit weight is ~300 g (with wraps).

There is a need to develop effective treatments for severe PTS that are well-tolerated and allow patients to carry on with their daily activities (6). In this clinical trial, we evaluate a novel device, *Venowave*TM, for the treatment of severe PTS.

Methods

We performed a randomized placebo-controlled, double-blinded 'cross-over' trial of patients with severe PTS at two Clinical Centres (Hamilton Health Sciences, Chedoke Division, Hamilton, Ontario; and the Thrombosis Unit, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Québec). The clinical trial protocol was approved by Health Canada (No. 64844) and the Research and Ethics Boards of both Clinical Centres. The study was registered with ClinicalTrials.gov (NCT00182208) and conducted according to the ICH-Good Clinical Practice guidelines for clinical trials.

Intervention

Venowave is a battery-powered lower limb venous return assist device developed by Saringer Research Incorporated, Stouffville, ON, Canada (Fig. 1). It consists of a rotating motor coupled with a wave-generating linkage to a planar plastic sheet, which is placed longitudinally on the posterior aspect of the calf and generates a wave-form motion on a flexible flat metal platform. This peristaltic pump (1 cm amplitude, 8 cm wide sinusoidal wave moving at 2 cm/sec) results in an upward, volumetric displacement of the wave at 16 cc/sec. It is attached firmly around the calf with a velcro support cuff and may be worn when mobile. The

cuff is adjustable to fit different leg sizes and can be adjusted to accommodate changes in leg swelling. *Venowave* is designed to counteract venous stasis and venous hypertension, etiological factors responsible for the development of PTS (13). In a previous study of 10 subjects with chronic limb edema, we demonstrated that wearing *Venowave* for 50 minutes (min) produced an 88% increase in duplex ultrasound-detected venous flow at the common femoral vein ($p=0.03$) (13). In a subsequent open-label pilot study (14), we demonstrated that *Venowave* resulted in a substantial clinical improvement of symptoms in four of six subjects with severe PTS (14).

All components of the control and active devices were identical, except for the connection between the motor and the planar sheet was inactive in the control device. Therefore, the control device was identical in size, weight and sound to the active intervention but did not generate a waveform motion. The control device produced some calf compression through added pressure from the cuff, and was therefore presented to the participants as one of two active interventions and not as a placebo.

Participants

Subjects over 18 years of age with PTS were potentially eligible if they had: i) a previous history of objectively-documented deep vein thrombosis; ii) daily leg swelling with discomfort (i.e. reported at least one of the following symptoms: heavy legs, aching legs and/or throbbing) for a minimum of 6 months that was considered due to PTS; and iii) Villalta scale score of greater than 14 (i.e. corresponds to severe PTS) (15).

Any patients who had: i) unstable symptoms (worsening, improving or variable over the previous month); ii) chronic lower limb edema from causes other than deep vein thrombosis; iii) active venous ulceration; iv) baseline calf circumference greater than 40 cm (cuff is too small); v) symptomatic peripheral arterial disease; or vi) peripheral neuropathy, were excluded. Current or prior use of graduated compression stockings did not influence eligibility.

Eligible, consenting subjects were allocated randomly in a 1:1 ratio to follow either Sequence 'A' (*Venowave* for 8 weeks in Period 1 followed by control for 8 weeks in Period 2), or Sequence 'B' (control for 8 weeks in Period 1 followed by *Venowave* for 8 weeks in Period 2). At the end of Period 1, participants had a four-week wash-out period before starting Period 2.

Devices were pre-packaged in pairs with each *Venowave* paired with a control device. Paired devices were labeled "A" and "B" corresponding to the order of use, and not related to whether they were active or control. Random allocation was determined by consecutively numbered patient kits that contained encrypted codes, corresponding to a randomly ordered pair of *Venowave* or control device. Upon obtaining written informed consent from an eligible participant, the research nurse opened the next patient kit in the sequence and provided the subject with device A. Participants were provided with device B at the end of the wash-out period.

All participants were instructed to put the device on each morning and to wear it for most of the day, for the duration of the study period. There was no restriction (upper limit) on the duration of use. Subjects were informed that the device could be worn when they were stationary or mobile and were taught how to use the de-

1. Over the past eight weeks, has the 'new treatment' been of benefit to you?

Yes No

2. a) If yes, how much have your leg symptoms improved since starting the 'new treatment'? (Circle)

1. A little better
2. Moderately better
3. A good deal better
4. A great deal better
5. A very great deal better

2. b) If no, how much have your leg symptoms worsened since starting the 'new treatment'? (Circle)

1. No change
2. A little worse
3. Moderately worse
4. A good deal worse
5. A great deal worse
6. A very great deal worse

3. Would you continue to use the 'new treatment'?

Yes No

Figure 2: Global rating instrument. The primary outcome was 'clinical success' defined as fulfilling all of the following criteria: 1) reported benefit from the intervention; 2) at least moderate improvement in symptoms of PTS; and 3) willing to continue to use the intervention.

vice i.e. method of application to leg, insertion of batteries, etc. They were also given instructions on maintenance of the device, and contact numbers in the event of a malfunction. The device was to be worn only on the leg exhibiting the PTS (i.e. the index leg).

Study subjects, investigators and research nurses were blinded to treatment allocation. To help maintain blinding, study participants were assessed at different times to each other and were asked not to discuss issues relating to the mechanical operation of the device with their clinicians. Both devices were called 'Venodevice' rather than *Venowave*, to avoid potential insights into the mechanism of action of the intervention.

Study measures

Four measurement instruments were used in this study. A global rating instrument was used to determine if each treatment phase was associated with a 'clinical success' (Fig. 2). Similar outcome measures have been used in two previous randomized trials in subjects with PTS (11, 12). The Villalta scale was used to measure the severity of PTS at baseline (inclusion criterion) and follow-up, and was a secondary outcome measure (15). This scale was designed to diagnose and rate the severity of PTS by quantifying five symptoms and six signs and has been used frequently in studies of patients with PTS. Higher scores indicate more severe PTS and a score of greater than 14 corresponds to severe PTS (maximum score of 33) (15). Although both legs were assessed, only the scores for the index leg were used in the analysis. The VEINES-QOL questionnaire was used to measure quality of life (QOL) (16). VEINES-QOL, a venous disease-specific quality of life instrument, has been shown to be reliable and responsive to change over time in patients with PTS (16, 17). VEINES-Sym is a validated subscale of VEINES-QOL that measures severity of venous symptoms. For VEINES-QOL and VEINES-Sym, higher scores indicate better quality of life. At

study end, participants were asked if they preferred the 'treatment intervention' in Period 1 or Period 2.

Data collection and follow-up

All data were submitted to the data-coordinating centre within the Clinical Trials Methodology Group, Henderson Research Centre, Hamilton, ON, Canada. They were responsible for maintaining the concealment of the random allocation sequence from investigators and patients. The study design, analyses, and decision to publish were all determined by the investigators.

Study participants were scheduled to attend four visits: 1) baseline; 2) at 8 weeks (prior to cross-over); 3) at 12 weeks (after the 4-week 'wash-out' period); and 4) at 20 weeks. The Villalta Scale and VEINES questionnaire were completed at all visits. The Global Rating Instrument was administered at the eight and 20 week follow-up visits; that is, at the end of each study period. Study participants were also asked to keep a diary of the number of hours they used the device each day.

Participants were screened clinically for recurrent venous thromboembolism and the development of venous ulceration at each visit. Adverse clinical events were adjudicated by a blinded expert in Thrombosis medicine. Serious adverse events were reported to Health Canada and the Research and Ethics Boards of both centres.

Outcomes

The primary outcome was 'clinical success' defined as fulfilling all of the following criteria: 1) the patient reported benefit from the intervention; 2) experienced at least moderate improvement in symptoms of PTS; and 3) was willing to continue to use the device (Fig. 2). Secondary outcome measures included each of the component clinical success responses, device preference, PTS severity (Villalta Scale score), venous disease-specific quality of

Table 1: Baseline characteristics.

Characteristic		
Number of patients	32	
Age (years) – mean (range)	50	(25–80)
Female gender – n (%)	16	(50)
Weight (kg) – mean (range)	89	(59–130)
Height (cm) – mean (range)	171	(152–188)
Body mass index ≥ 25 – n (%)	25	(78)
DVT diagnosis (years) – mean (range)	5.2	(0.7–17.7)
Villalta Scale score – mean (range)	20	(13–33)
Graduated compression stockings – n (%)	26	(80)
Pneumatic compression pumps – n (%)	1	(3)
Physical demands of typical day – n (%)		
– Low	8	(25)
– Medium	13	(41)
– High	10	(31)
Avg. daytime hours standing – mean (range)	7.8	(3–18)
Avg. daytime hours sitting – mean (range)	8.0	(1–14)
Left leg with PTS – n (%)	26	(81)

life (VEINES-QOL) and severity of venous lower limb symptoms (VEINES-Sym).

Statistical analysis

Sample size was calculated for the primary binary outcome measure. From our preliminary pilot study (14), we estimated a probability of clinical success with the active device of 67% in subjects with severe PTS. Based on previous research in this field, we expect a placebo effect of approximately 20%. We considered a minimum clinically important difference to be an additional absolute probability of clinical success of 40%, that is a probability of clinical success of 60% of clinical success with the active device ($\text{Chi}^2=0.05$, two-sided; power=80%). Taking into account loss to follow-up (10%), we required a total sample size of 32 subjects.

The paired binary outcomes were analyzed primarily using McNemar's tests, and secondly, using logistic mixed models to account for correlation and period effects, and also to assess the impact of potentially influential baseline covariates: gender, body mass index (BMI), education, swelling, compression stockings use. The paired continuous outcome measures (Villalta and VEINES scale scores) were analyzed primarily using paired t-tests, and secondly, using linear mixed models to account for correlation, baseline scores and a period effect, and an extended model adding the covariates listed above. P-values less than 0.05 were considered to be statistically significant. All statistical analyses were performed using SAS version 9.1 (Cary, NC, USA).

Results

Between February 2004 and October 2005, 32 patients were recruited. The baseline characteristics of participants are presented in Table 1. Mean age was 50 years, and 50% were women. Most (80%) participants were using graduated compression stockings at the time of recruitment. Twenty-six participants completed the trial (Fig. 2). Three participants withdrew during Period 1 (one patient died, two experienced side effects possibly related to the device), two withdrew during the wash-out period (one suffered from depression, one withdrew to provide care to an ill spouse), and one patient withdrew during Period 2 (experienced side effects possibly related to the device) (see *Adverse Events*) (Fig. 3) Mean duration of use (per day) was 6.2 hours (h) (SD 3.4) for *Venowave* and 5.3 h (SD 3.1) for control.

Clinical success

A clinical success was reported in 10 participants using the *Venowave* device, and in four patients using the control device; two of these participants reported a clinical success with both devices ($p=0.11$). In the two patients who reported a clinical success with both devices, one had a preference for *Venowave* and one a preference for control. Fourteen participants (54%) did not report a clinical success to either device (Table 2). Graduated compression stockings were worn by five of the eight participants who reported a clinical success with *Venowave* alone, and in all participants who reported either a clinical success with the control device alone ($n=2$) or with both devices ($n=2$). The logistic modeling of clinical success produced stronger treatment effects ($p=0.068$ for the multivariable model adjusting for period effect and baseline covariates), but showed no evidence of period or baseline covariate main effects.

Secondary outcomes

Table 2 also presents a summary and analysis of the components defining clinical success, and patient device preference. The trend in favor of *Venowave* was consistent across all three components; however, only the "benefit" component showed a strong treatment effect. There was a non-significant benefit associated with *Venowave* for the composite outcome of "benefit" from the device and willing to "continue to use" the device, reported in half of the participants using *Venowave*. Nineteen participants preferred the *Venowave* while only four preferred the control device; three preferred neither ($P=0.003$).

The VEINES questionnaire and Villalta scale were completed fully at all four follow-up assessments by 24 and 25 participants respectively. Mean VEINES-QOL score at the end of study period was significantly greater ($P=0.004$) for *Venowave* (52.5; SD 5.8) compared to control (50.2; SD 6.2). Mean Villalta scale score at the end of study period was significantly reduced for *Venowave* (12.2; SD 6.3) compared to control (15.0; SD 6.1); $p=0.004$ (see Table 3). After adjustment for baseline scores, period effect and baseline covariates in the mixed model, all treatment effect analyses remained consistent with the results of the paired t-tests. There was no evidence of a "carry-over" effect for any outcome measure.

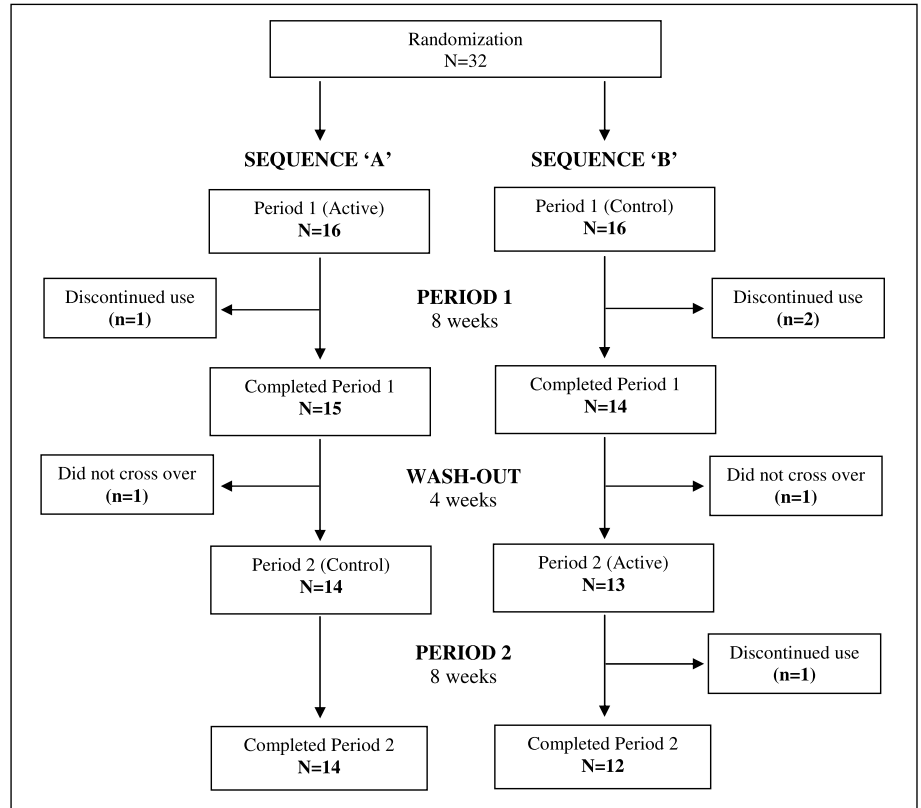


Figure 3: Study flow.

Table 2: Primary outcome results.

Patient-reported outcome	Venowave™ alone	Control alone	Both devices	Neither device	P-value*
Clinical success†	8	2	2	14	0.11
(1) Benefit reported with device	12	3	6	5	0.035
(2) Moderate or greater improvement in leg symptoms	8	2	3	13	0.11
(3) Willing to continue to use device	11	5	3	7	0.21
Other outcomes					
(4) Benefit and continue to use‡	11	4	2	9	0.12
(5) Preferred device	19	4	0	3	0.003

†Requirement for clinical success: outcomes (1) and (2) and (3). ‡Composite of outcomes (1) and (3). *McNemar's test.

Adverse events

One patient died during week 8 (control device period). The patient did not complete Period 1 and was not wearing the device at the time of death. Cause of death was deemed to be cardiac and unrelated to the study. The patient did not have an autopsy, but the case was reviewed by the local Coroner. Clinical details were also presented to the local Research and Ethics Boards and Health Canada and determined to be unrelated to the study device. No cases of recurrent venous thromboembolism were reported. One participant withdrew from the trial because of active

venous ulceration that occurred after a minor injury while wearing the control device. He discontinued wearing the device after the injury, and the small area of ulceration was attributed to the injury and was deemed to be unrelated to the study device. Three other participants reported side-effects, deemed to be 'non-serious' and related or possibly related to the device. All three participants withdrew from the trial. One participant reported 'leg swelling, irritation and superficial bleeding', one reported 'skin irritation' and one reported 'leg swelling with itching of skin'.

Table 3: Secondary outcome results.

Outcome measure	Mean score (SD)				
	Baseline n=26	Venowave™ n=26	Control n§	Difference n§	P-value*
VEINES Questionnaire†					
VEINES-Sym	48.6 (5.3)	52.7 (6.9)	50.0 (7.2)	+3.3 (5.9)	0.01
VEINES-QOL	48.3 (4.4)	52.5 (5.8)	50.2 (6.2)	+2.9 (4.5)	0.004
Villalta Scale‡					
Symptoms component	10.1 (2.7)	6.1 (3.2)	8.5 (3.9)	-2.4 (2.9)	0.0003
Signs component	9.0 (2.3)	6.1 (4.3)	6.6 (3.5)	-0.6 (3.6)	0.4
Total Villalta Score	19.1 (3.4)	12.2 (6.3)	15.0 (6.1)	-3.1 (4.9)	0.004

SD=standard deviation; QOL=quality of life. § n=26 for Villalta symptoms, n=25 for Villalta signs and total, n=24 for VEINES. *paired t-test for difference between Venowave™ and control. † The Venous Insufficiency Epidemiological and Economic Study (VEINES) questionnaire consists of 26 items, 10 items measure severity of symptoms, 9 items measure limitations of daily activity, 5 items measure the psychological impact of venous disease and 2 items cover time of day that symptoms are most severe and change over the past year. Summary score may be computed in 2 ways: 1) VEINES-Quality of life (QOL), that includes 25 items and, 2) VEINES-symptoms that includes 10 items relating to severity of symptoms. The item measuring time of day of maximal symptoms is not included in either summary measure. As the number of response categories varies between questions, summary (mean) scores are calculated by a transformation to z-score equivalents and then to a t-score with mean=50 and SD=10. Lower scores indicate more severe PTS. ‡ The Villalta scale consists of 11 items, 5 covering symptoms and 6 covering lower limb signs (e.g. skin discoloration, swelling). Summary scores may be presented as a total score (maximum of 33 points) or divided into sub scores based on assessment of symptoms and signs of PTS. Higher scores indicate more severe PTS.

Discussion

In this randomized controlled trial of patients with severe PTS, almost 40% of patients treated with *Venowave* reported a meaningful clinical response. In addition, there was a statistically significant improvement in severity of PTS and venous disease-specific quality of life with *Venowave* treatment compared to control. The change in VEINES-QOL and VEINES-Sym scores with *Venowave* in our study are similar to the clinical change observed in a prospective cohort study of patients with symptomatic improvement after acute DVT (between 1 and 4 months) (17).

Although not statistically significant for the primary composite outcome, we believe that these findings are of considerable clinical importance. Severe PTS is responsible for substantial personal disability, work absenteeism, reduced quality of life and increased health care costs (3–8). The mainstay of current therapy, graduated compression stockings, is often of limited benefit in patients with severe PTS (11). In this study, most patients were using compression stockings at the time of recruitment but continued to have severe symptoms despite their use. Importantly, most patients who reported a benefit with *Venowave* were also using graduated compression stockings concomitantly. Therefore, *Venowave* can be used alone or in conjunction with graduated compression stockings. Compared with pneumatic compression pumps (12), *Venowave* allowed patients to remain mobile, and the device improved, rather than interfered with, activities of daily activities during use.

Venowave appears to be safe. The most common side-effects attributed to *Venowave* were heat sensation, skin irritation and increased sweating. No cases of recurrent venous thromboembolism were reported during the study period. However, since this was a small study, and the duration of follow-up in this trial was

limited to eight weeks, further prospective studies are required to determine the long-term safety and tolerability of *Venowave*.

Although every effort was made to maintain blinding of study participants and research nurses, it is likely that participants were aware of a difference between the active and control devices, given the mechanical nature of the intervention. In addition to a placebo effect, we expected the control device to have an active component, namely added leg compression with planar calf support during standing and walking. We, therefore, presented the control device as an alternative ‘active’ device rather than placebo. Four participants reported a clinical success with the control device, two of which also had a clinical success with *Venowave*. Our choice of control device would be expected to increase the likelihood of not finding a treatment effect when one truly existed (i.e. type II error), undermining our ability to detect a statistically significant benefit with *Venowave*.

The main limitations of our study are the small sample size and short duration of follow-up. That said, this study is the largest clinical trial of treatment of severe PTS. Further studies are required to determine the longer-term benefits and safety of *Venowave*. Strengths of the study are that participants, investigators, assessors and data analyzers were all blinded and that validated scales were used to assess clinical outcomes.

In conclusion, *Venowave* appears to be a very promising new therapy for severe PTS, a chronic disabling condition with limited treatment options. In our study population of patients with severe PTS, refractory to standard therapies, almost 40% of patients reported clinical improvement with *Venowave*.

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