A comparative study investigating the effectiveness of neuromuscular electrostimulation versus intermittent pneumatic compression in enhancing lower limb blood flow in healthy subjects

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Abstract:

Objectives: This study compared the effectiveness of a neuromuscular electrostimulation device (geko™ T-1) in enhancing lower limb blood perfusion with two leading IPC devices; the Huntleigh Flowtron Universal™ ("IPC-HF") and the Kendall SCD™ ("IPC-Kendall"). The subject's tolerance and acceptability to the devices were also compared. **Methods:** Ten healthy volunteers were recruited in the study. The devices were fitted bilaterally, in a sequential manner. Vital signs together with ultrasound and laser Doppler fluxmetry (LDF) assessments were performed. **Results:** The use of the geko™ T-1 device, was superior to the IPC devices in increasing both venous and arterial blood volume flow by ~30% ($p \leq 0.001$). The geko™ T-1 device increased arterial blood velocity by 24% ($p \leq 0.001$). A substantial increase in the total microcirculatory blood velocity by ~370% was reported following the use of the geko™ T-1 device ($p \leq 0.001$). When using visual analogue scale no significant differences in discomfort were found between the geko™ T-1 device and IPC devices ($p > 0.05$). **Conclusion:** The geko™ T-1 device is more effective in increasing total lower limb perfusion. It is superior to the IPC devices in increasing venous, arterial and microcirculatory blood velocity. Both the devices studied were safe and were well tolerated by healthy subjects.

Introduction

In recent years, mechanical prophylaxis for the prevention of deep vein thrombosis (DVT) has enjoyed wide popularity, as its use is not associated with the adverse events seen with pharmacological prophylaxis (1). Intermittent pneumatic compression (IPC) is one of the most commonly used mechanical prophylaxis methods. All IPC devices have the same general objective, limb compression, to expel blood from the underlying superficial and deep veins, which, if the valves are competent will be displaced proximally (1).

Other methods for the prevention of DVT include direct electrical stimulation of the lower limb muscles, which has also been shown to be an effective modality in improving blood flow (2-4) Electrical Stimulation has also been shown to reduce the incidence of DVT at least as well as other forms of mechanical compression (5-8). However, the enhanced level of discomfort associated with their use, has, until recently, limited the application of such techniques in clinical practice. Therefore, developing an alternative technique that is effective and easy to use is justifiable.

A novel neuromuscular electrostimulation medical device (geko™ T-1) has been developed by Firstkind Ltd, High Wycombe UK to provide the benefits of electrical stimulation but without the previously associated discomfort levels. The system operates using OnPulse™ Technology, activating the calf and foot pumps of the leg by low intensity neuromuscular electrical nerve stimulation of the common peroneal nerve located in the region ofthe popliteal fossa (9). Furthermore, in early clinical development, the system was found to be well tolerated. The geko™ T-1 device has been CE Marked and its intended use is to improveblood circulation, and for DVT prophylaxis. It consists of 7 pulse widths, ranging from 70µs to 560µs. The desired pulse width can be selected by an on-off switch button.

Objectives

The purpose of this study was to compare the effectiveness of a novel medical device, geko™ T-1 (Firstkind Ltd, UK) at a Threshold and Normal Clinical Use settings in enhancing lower limb blood perfusion with two leading IPC devices, Huntleigh Flowtron Universal™ (Huntleigh Healthcare Ltd, UK) and Kendall SCD Express™ (Covidien plc, Ireland). Furthermore, subjects' tolerance and acceptanceto the devices will be compared using a discomfort questionnaire.

Methodology

Subjects

Ten healthy volunteers, aged between 18 and 65 years were recruited to participate in the study. The study was approved by the North London Research Ethics Committee 1 (reference 05/Q0408/14). Volunteers were instructed to have a light breakfast and avoid fatty foods and caffeine containing products. Volunteers were provided with study information sheets, and written informed consent was obtained prior to the study. Initially a screening evaluation was performed, which included a medical history, physical examination and colour flow duplex ultrasound of the lower legs to exclude the presence of pre-existing DVT. The specific inclusion and exclusion criteria are presented in the tables 1 & 2.

Study Methodology

All examinations were performed in a room where the temperature and humidity were controlled (24 $\pm 1^0$C, relative humidity 30-40%). Subjects clad in shorts, lay supine on a padded table that could be tilted manually, with their heads supported by a pillow and tilted upwards to 45°. After 30 minutes of supine rest, baseline measurements were recorded. Test devices were then fitted bilaterally to the subject's legs, in accordance to the manufacturer's instructions, in a sequential manner. The order of the device tested was made in accordance to a pre-set randomisation schedule to reduce bias. Based on previous findings, each device was active for a period of 30 minutes followed by a 10 minutes recovery phase, to allow vascular re-equilibration prior to applying the next device(9). At the end of each programme and while the devices are still active, changes in blood flow and volume, together with microcirculatory velocity were measured using colour flow duplex ultrasound (Philips IU22; Philips Healthcare, USA) and laser Doppler fluxmetry (Laser Doppler Perfusion & Temperature Monitor DRT4; Moor Instruments Ltd, UK). Several safety assessments were also performed, including measuring blood pressure using a digital blood pressure monitor

(UA-767PC; A&D Instruments Ltd, UK), measuring transcutaneous oxygen tension (TCM4 Tina; Radiometer Ltd, UK) and pulse oximetry (3900P TruTrack®+ Datex-Ohmeda Ltd, UK).

At the end of each program, subjects were asked to evaluate their acceptance and tolerance to each device using a discomfort questionnaire. Maximum discomfort was compared to a blood pressure cuff inflated around the upper arm. Subjects rated their discomfort levels using a visual analogue scale (VAS) by marking the level of the perceived pain along a 100 mm line, marked at one end "no sensation" and at the other end "severe discomfort". Also a discrete five category verbal rating scale (VRS) was also used to select the appropriate category of the perceived discomfort, where"1 = no sensation (other than muscle tensing and relaxing)", "2 = minimal sensation", "3 = mild discomfort", "4 = moderate discomfort", or "5 = severe discomfort". At the end of the assessments, the subject's deep veins were re-examined with duplex ultrasound to exclude the development of DVT.

Electrical Nerve Stimulation using the geko™ T-1 device

Transcutaneous electrical nerve stimulation was performed using a novel device (geko™ T-1, Firstkind Ltd, UK) (Figure 1). The geko™ T-1 device is a small, disposable, internally powered, self-adhesive system that is applied over the common peroneal nerve (also called the lateral or medial popliteal nerves) located in the region of the popliteal fossa that wraps around the fibular head near the knee.These nerves innervate the lower limb musculature, with the resulting stimulation causing isometric contraction of the anterior and posterior calf and foot muscles. Table 3 lists the specifications and settings of the device. Stimulation of these nerves by the geko™ T-1 device results in isometric contraction of the muscles that enhances blood flow from the lower limbs back to the heart, thus increasing venous return (9). The device has 7 stimulation settings relating to pulse width ranging from 70 to 560µs, set by the on-off switch and indicated by a flashing light (setting 1 = lowest; setting 7 highest). Unlike many electrostimulation devices, the device operates at a fixed frequency (1Hz) with a constant pulse current of 27mA. The geko™ T-1 devices were applied bilaterally to each subject according to the instructions for use manual supplied. For each subject, the device was initially set to a threshold setting (geko™-TS) (as defined as the minimum setting to elicit a minor muscular contraction in both the calf and the foot) for a period of 30 minutes followed by 10 minutes rest (9). Following the 10 minute period of rest,

a Normal Clinical Use (geko™-NCU) setting was selected that was characterised by 3 additional levels to the previous threshold setting.

Intermittent Pneumatic Compression (IPC)

The two intermittent pneumatic compression devices used in this study were the Huntleigh Flowtron Universal™ (IPC-HF) and Kendall SCD Express™ (IPC-Kendall). Each device was applied bilaterally by a trained staff to the calf as per the manufacturer's instructions. The devices differ in their pumping cycle. The IPC-HF device has a pumping cycle characterised by 13 seconds of inflation period and 47 seconds deflation period. In contrast, the IPC-Kendall has approximately 12 seconds inflation and 48 seconds deflation period; the periodicity of the cycling of this device is influenced by venous refilling times. The compression pressure was kept the same for both IPC devices (40 mmHg).

Ultrasound Assessments

Colour flow duplex ultrasound measurements were performed (Philips IU22; Philips Healthcare, USA) by an accredited vascular ultrasonographer. Measurements to the superficial femoral vessels (arterial and venous) were then taken bilaterally; at baseline and following the completion of each programme (while the device was still active). The following parameters were studied: peak maximum velocity, vessel diameter, and volume flow. Estimations of these parameters were obtained bilaterally for a duration of 15 seconds Venous volume flow measurements using IPC devices are usually presented incorrectly accounting for the inflation cycle only, thereby significantly over estimating their true effect. Thus, calculations were performed for venous volume flow measurements according the underlying formula, in order to obtain the exact volume flow per minute to account for the difference in the inflation/deflation cycle.

$$Venous\ Volume\ flow\ per\ minute = \frac{Inflate\ venous\ blood\ volume}{60\ seconds/inflation\ time} + \frac{Deflate\ venous\ blood\ volume}{60\ seconds/deflation\ time}$$

Data Analysis

All assessments were acquired at baseline (resting blood flow corresponding to cardiac output and respiration) and at the end of each programme for each device. Statistical analysis was performed using Minitab 16 software (Minitab Ltd, UK). Analysis of variance using adjusted

sum of squares was conducted for each parameter tested. A p-value of ≤ 0.05 was considered statistically significant. Data shown in the results section represent the mean of data obtained from the 10 volunteers studied.

Results

Ultrasound Assessments

A. Mean Blood Volume Flow

Analysis of the data using linear models indicated that there is a highly significant difference in both venous and arterial blood volume flow between the devices ($p \leq 0.001$). The highest median value was achieved following the use of the geko™ T-1 device. The median (IQR) values of the venous blood volume flow were 123.5 mL/min (73.4) at baseline, 163 mL/min (105.3) following the use of the geko™ T-1 device at Normal Clinical Use setting, 129 mL/min (42.7) following the use of the geko™ T-1 device at threshold setting. In contrast, measurements following IPC devices were 118 mL/min (72.7) following the use of the IPC-HF, and 115 mL/min (60.2) following the IPC-Kendall device (Figure 2).

As with the arterial volume flow measurements, the median (IQR) values were 197.5 mL/min (135.8) at baseline, 244.5 mL/min (125) following the use of the geko™ T-1 device at Normal Clinical Use setting, 170 mL/min (107.5) following the use of the geko™ T-1 device at threshold setting, 181.5 mL/min (70.5) following the use of the IPC-HF, and 158 mL/min (73) following the IPC-Kendall device (Figure 3).

Considering the average percentage change in comparison to baseline for venous blood flow measurements, the highest average percentage change was achieved following the use of the geko™ T-1 device at Normal Clinical Use setting (33%), followed by the geko™ T-1 device at threshold setting (14%). Surprisingly, both IPC devices demonstrated similar values below baseline levels (-4%).

Equally, when examining arterial blood flow the highest average percentage change was obtained following the use of the geko™ T-1 device at Normal Clinical Use setting (30%). However, unlike the venous volume flow measurements, the use of the geko™ T-1 device at the threshold setting reported a slight decrease in the percentage change below baseline (-7%) that was roughly similar to that reported following the use of the IPC-HF device (-9%); with the lowest percentage change reported for the IPC-Kendall device (-16%).

B. Mean Blood Velocity

Blood velocity measurements for IPC devices were made during both the inflation and deflation phase, taking into consideration the marked difference in the compression cycles between the geko™ T-1 device and the IPC devices. The geko™ T-1 device accelerates consistently every second (1Hz) unlike the IPC devices, which accelerate only during the inflation period (Figures 4 - 6). Results obtained following analysis of variance showed a highly significant difference between the devices, $p \leq 0.001$. Analysis of venous velocity measurements, revealed a substantial increase of 174% following the use of the geko™ T-1 device at Normal Clinical Use setting, which was equivalent to the IPC devices; 166% and 143% for IPC-HF and IPC-Kendall respectively. A 73% increase was reported following the use of geko™ T-1 at threshold setting.

The median values reported following the use of the geko™ T-1 at Normal Clinical Use setting were equivalent to that of the IPC devices during the inflation phase. The median (IQR) for venous velocity measurements were 13.8 cm/sec (5.4) at baseline, 38.3 cm/sec (10.35) following the use of geko™ T-1 at Normal Clinical Use setting, 22.0 cm/sec (12.75) for the geko™ T-1 at the threshold settings, 37.0 cm/sec (14.25) and 33.70 cm/sec (14.63) for IPC-HF and IPC-Kendall during Inflation phases. In contrast, during the deflation phases, the median (IQR) values reported were 14.7 cm/sec (8.35) for the IPC-HF and 12.6 cm/sec (5.2) for the IPC-Kendall device (Figure 7).

Similarly, when measuring the arterial velocity, the highest increase reported was following the use of the geko™ T-1 device at Normal Clinical Use setting, where the velocity increased by 24% compared to baseline. A small increase was observed for the geko™ T-1 device (2%) when used at threshold setting. In comparison, a decrease was observed following the use of the IPC-Kendall by -1% during the inflation phase, and a further decrease following the use of IPC-HF device by -4% during inflation phase.

The median (IQR) obtained was 83.15 cm/sec (24.23) at baseline, 98.25 cm/sec (27.70) following the use of the geko™ T-1 device at Normal Clinical Use setting, 84.75 cm/sec (22.10) for the geko™ device at the threshold setting, 81.90 cm/sec (20.40) for IPC-HF during the inflation phase and 80.30 cm/sec (17.85) for IPC-Kendall during inflation phase (Figure 8).

C. Mean Vessel Diameter

No significant difference in mean femoral vessel diameter was reported between the devices studied $p > 0.05$. Both venous and arterial measurements remained stable throughout the study.

D. Skin Microcirculatory Assessments

Microcirculatory assessments using laser Doppler fluxmetry (LDF) showed a highly significant difference between the devices, $p \leq 0.001$. The use of the geko™ T-1 device at both settings showed a highly significant increase in microcirculatory blood velocity by 394% and 345% respectively. This is compared to a 44% increase following the use of IPC-HF device and a modest 59% increase achieved following the use of IPC-Kendall (Figure 9).

The median (IQR) range obtained was 9.45 (7.61) at baseline, 35.46 (24.26) following the use of the geko™ T-1 device at Normal Clinical Use setting, 27.13 (24.92) for the geko ™ T-1 device at threshold setting, 6.67 (7.89) for IPC-HF, and 6.71 (12.58) for IPC-Kendall device.

E. Safety Assessments

No significant difference was reported between the devices following the measurement of blood pressure, transcutaneous tissue oxygen ($TcPO_2$), tissue oxygen saturation (SPO_2) as well as heart rate, $p > 0.05$. All measurements remained equally stable throughout the study.

F. Discomfort Assessments

Analysis of the discomfort levels reported following the use of each device was not significant using the visual analogue score, $p > 0.05$, but showed a statistically significant difference using the verbal rating score, $p \leq 0.05$ (Figures 10 & 11). Using the verbal rating score, the discomfort level following the use of the geko™ T-1 device at the Normal Clinical Use setting was only rated as mild discomfort as compared to the other devices studied, which were rated at a minimal sensation.

Discussion

The present study compares the effectiveness of an electrical nerve stimulation technique with IPC devices. Maintaining adequate peripheral blood flow in the lower limb is essential to prevent venous stasis, hence reducing the incidence of DVT. The devices in this study may be considered effective in preventing venous stasis; however they differ in the magnitude of increase in lower limb blood perfusion (1, 9, 10).

Based on the analysis of the data obtained from the study subjects, it can be inferred that the novel device studied (geko™ T-1), is in many ways superior to IPC Huntleigh Flowtron™ and IPC Kendall SCD™ devices in enhancing blood flow in the lower limbs. This is evident from the substantial significant increase in the femoral venous and arterial blood flow volume by ~ 30% following the use of the geko™ T-1 device. Although the volume flow increase following the use of the geko™ T-1 device at the threshold setting is, as expected, less than that of the Normal Clinical Use setting , it was still much greater than that reported following the use of the IPC devices, where a decrease in total volume flow was observed. Therefore, it appears that the continuous stimulation evoked by the novel technology studied, may be more efficient in ejecting a greater blood flow through both the femoral vein and artery than that ejected during the relatively short inflation period used by the IPC devices.

Measuring arterial peak velocities, demonstrated that the use of the geko™ T-1 device is more effective than IPC devices in producing an increase in the femoral artery. This is in comparison to a fall in arterial velocity following the use of IPC devices, which may be of concern especially in patients with peripheral arterial disease. Furthermore, our data shows that the geko™ T-1 device is as efficient as the IPC devices during the inflation period in increasing peak venous velocity. Although the use of the geko™ T-1 device at the threshold setting demonstrated, as one would expect, lower increase (73%) as compared to an increase by 174% at the Normal Clinical Use setting, it is still considered more effective than the IPC devices. The use of IPC devices showed an increase by 11% only for IPC-HF and a fall by 9% for IPC-Kendall. The results obtained further confirms that the continuous acceleration in velocity for the geko™ T-1 device (every second) compared to an acceleration every minute by the IPC devices is more effective in enhancing blood flow, hence preventing venous stasis.

Peak venous velocities are considered a “unique selling point” by some of the manufacturers to indicate the efficacy of their systems. However, there is a scarce evidence that such systems that produce higher velocities during compression, yield low DVT rates, a study

published by Proctor et al suggests the opposite (1, 11). Published data have shown that the use of IPC devices at pressures of 40 mmHg, achieves a calf compression between 35 to 60 cm/sec (1, 12-15). The results obtained from our study are in agreement with those figures, as the mean velocity range obtained following the use of IPC-HF and IPC-Kendall during the inflation phase is 36 and 33 cm/sec respectively.

Laser Doppler fluxmetry, which reflects the microcirculatory blood velocity in the skin, is based on measuring the light scattered from the tissue by moving red blood cells that undergoes a frequency shift proportional to the velocity of the moving objects A highly significant increase by ~ 370% was demonstrated following the use of the geko™ T-1 device, in comparison to a modest 59% and 44% increase following the use of IPC-HF and IPC-Kendall devices respectively. Interestingly, some studies have indicated the efficacy of electrical stimulation in wound care by increasing blood flow and enhancing tissue oxygenation, thereby targeting inflammation and proliferation phases of wound healing (16-18). Thus, the vast increase reported in laser Doppler fluxmtery values together with the tissue oxygen results, may indicate the potential benefits of the geko™ T-1 device in lower limb wound care. Further studies are being carried out to confirm this.

Moreover, safety parameters were measured to compare the safety of the geko™ T-1 device to the IPC devices. Pulse oximetry measurements confirmed a stable heart rate and saturated oxygen levels throughout the study. No significant difference ($p > 0.05$) in heart rate and mean oxygen saturation were reported between the geko™ T-1 device and IPC devices. This may be considered a further non-subjective assessment of subject tolerance and potential compliance. Transcutaneous tissue oxygen levels also remained stable throughout the study, Furthermore, blood pressure measurements showed no differences. This again is a significant indicator of the safety of the device. Duplex ultrasound measurements of the arterial and venous femoral vessel diameter also showed no significant change throughout the study, which confirms the validity of the ultrasound volume and velocity measurements.

Significant pain due to high intensity settings has been a major hurdle to the development of electrical stimulation technology, especially direct muscle stimulation. In many cases this has limited their application and clinical usage to the anaesthetised patient. In contrast, discomfort assessment by VRS showed that the use of the geko™ T-1 device at Normal Clinical Use setting is associated with only a mild discomfort, and a minimal sensation perceived following the use of IPC devices as well as the geko™ T-1 device at the threshold

setting. It is essential to note that the devices were active for a short period of time (30 minutes), thus the mild discomfort reported following the use of the geko™ T-1 device at Normal Clinical Use setting, might decrease over time due to normal neurological habituation response.

Moreover, clinical experience using IPC devices has indicated that longer term use of such devices may lead to decreased compliance due to perspiration under the cuffs, loosening of the cuffs due to oedema reduction leading to decrease in efficacy and the effect of 'tethering' to the control module. On the contrary, the geko™ T-1 is small, self-contained and unobtrusive device that enhances lower limb blood perfusion thereby preventing venous stasis., while encouraging complete patient mobility.

Conclusion

The present study is the first to compare the effectiveness of a portable self-contained electrical stimulation device to the widely used intermittent pneumatic compression systems. The findings of the study indicate the potential benefits of using electrical nerve stimulation technology in improving circulatory dynamics in the arterial, venous and microcirculatory vasculature of the lower limb. In particular reference to DVT prophylaxis, the geko™ T-1 device significantly enhances venous return and reduces venous stasis in comparison to IPC systems as shown by the significant increase in femoral volume flow and velocity. The stimulation applied was perceived by healthy subjects as acceptable, as only mild/minimal discomfort was associated with its use. We propose that the novel device has a significant potential for the development into an easy-to-use, pain-free device, with a potential use in the prevention of DVT and management of several other vascular disorders. The geko™ T-1 device portability is also of major interest within the clinical environment as it will facilitate greater patient mobility than IPC systems. Further studies investigating the compliance of nurses as well as patients to the geko T-1 device will be conducted. Additional large scale studies are underway to further explore its advantages and to provide evidence on its effectiveness to prevent DVT. Moreover, tudies are underway to assess longer term usage of the geko™ T-1 device in surgical and medical patients, particularly in patient groups where IPC devices are contraindicated or impossible to use (such as fractures).

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Conflict of Interest

The author has no financial or proprietary interest in the subject matter or material discussed. Drs Arthur Tucker and Duncan Bain are named inventors of the nerve stimulation technology described in this study, on behalf of Sky Medical Technology.

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