Abstract

Aim

The aim of this feasibility study was to investigate the potential role of a novel neuromuscular electrical stimulation (NMES) device in preventing the formation of oedema following total hip replacement (THR).

Methods

Successive primary THR patients were recruited into a randomised controlled trial. Participants were randomised to wear either the NMES device or compression stockings continually from post-surgery until discharge.

The main outcome measure was presence of lower limb oedema, assessed by taking measurements of the circumference of the ankle, knee and thigh on the operated leg and non-operated leg, pre-operatively, post-operatively, at two days post-operatively and every day until discharge. Secondary objectives were to compare adverse events, the presence of asymptomatic and symptomatic deep vein thrombosis (DVT) and device tolerability between groups.

Results

Data from 40 participants were analysed (NMES (n = 20), compression stockings (n =20)). The NMES group had significantly less oedema and the device was found to be tolerable and safe.

Conclusion

The results of this study suggest that the NMES is a safe and well tolerated alternative to compression stockings, which should be considered by clinicians

seeking the additional benefit of reducing post-operative oedema. In addition the NMES device should be considered as part of a DVT prophylaxis.

INTRODUCTION

Total hip replacement (THR) is a common and successful surgical solution for the treatment of osteoarthritis of the hip. The procedure has demonstrated positive results for patients and the development of surgical techniques, pain management strategies and enhanced recovery after surgery (ERAS) pathways have improved outcomes further (Ibrahim et al. 2013). Length of stay has reduced (den Hartog et al. 2013) and return to function has been accelerated with no increase to post-operative complications or re-admission rates (Husted et al. 2008). In addition, outpatient THR has been considered feasible in selected (den Hartog et al. 2015) and unselected patients (Gromov et al. 2017),

However, some issues still remain for patients post-surgery. Husted et al. (2011) found the main clinical reasons for delayed discharge following THR to be pain, dizziness and general weakness. Decreased muscle function or weakness immediately post-op is unlikely to be due to atrophy alone, and the formation of oedema post-operatively is widely accepted to lead to pain and to exacerbate loss of muscle function. Clinically, oedema is described as an abnormal build-up of interstitial fluid in the body that is enough to produce palpable swelling (Kerchner et al. 2008). In addition to surgical trauma, decreased mobility immediately post-operatively can lead to a reduction in venous return, preventing the movement of fluid from tissues back into blood vessels (Kerchner et al. 2008). This creates an imbalance between capillary filtration and lymph drainage, leading to swelling.

Currently, there is limited evidence that describes the effect of oedema on recovery, or what percentage of patients develop lower-limb oedema following THR. Traditional treatment methods for oedema following total knee replacement (TKR)

may include cooling or cryotherapy, early ambulation, elevation of limbs, compression stockings and massage to help stimulate the release of excessive fluids.

An alternative treatment method is neuromuscular electrical stimulation (NMES), which stimulates nerves to activate muscle, and has been shown to enhance venous blood flow and reduce oedema in non-hip replacement populations (Doran & White 1967; Dejode et al. 1973, Faghri et al. 1997, Broderick et al. 2010, Tucker et al. 2010). However, the clinical application of NMES for post-surgical oedema prevention has been limited until now due to concerns over perceived discomfort and the impractical design of devices (Broderick et al. 2011). A number of studies have demonstrated that NMES significantly improves blood flow in the deep veins, (Faghri et al. 1997, Broderick et al. 2010, Tucker et al. 2010, Browse & Negus, 1970, Dejode et al. 1973) and the NMES device has been found to increase blood flow in the deep veins of the calf (Griffin et al. 2016). Recent developments in the design of NMES devices have significantly increased patient comfort and tolerance of NMES by allowing effective stimulation with lower current density and pulse duration (Broderick et al. 2011). These improvements in comfort have been further developed by utilising indolent nerve stimulation in place of direct muscle stimulation (Browse and Negus 1970).

The primary objective of this study was to evaluate whether an NMES device is more efficient than compression stockings (Thromboembolic deterrent stockings (TEDS)) in preventing the formation of oedema following THR surgery. Compression stockings were chosen as the comparator as they are routinely used in the study site for the prevention of lower limb oedema and DVT. Secondary objectives were to compare the formation of asymptomatic and symptomatic DVT, to compare device acceptability, tolerability and compliance, and to compare device safety by monitoring for adverse events.

METHODS

This was a randomised open label study comparing NMES and compression stockings with full ethical approval granted by the National Research Ethics Service (NRES) (REC reference 13/LO/0059, Protocol number FKD-TEDS-001, IRAS project ID 117650). The study was conducted in accordance with the principles of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and in compliance with European Standard ISO 14155:2011 Clinical Investigations of Medical Devices for Human Subjects – Good Clinical Practice. It was registered on ClinicalTrials.gov (Identifier: NCT01935414). The study is reported according to CONSORT guidelines for reporting randomised controlled trials (CONSORT, 2017).

Consecutive primary THR operations performed by a single surgeon at a private hospital were screened for eligibility in accordance with the inclusion and exclusion criteria detailed in Table 1. Recruitment continued until 40 patients had completed the trial. Eligible patients who consented to take part in the study were randomised by a clinical researcher with a 1:1 allocation via a sealed envelope prepared by an

112 independent Clinical Research Organisation. All participants followed the standard
113 care pathway for hip replacement and received the standard care for oedema
114 prevention before surgery, during surgery and on discharge. The only difference in
115 treatment between the two groups was that from post-surgery until discharge the
116 participants were randomised to receive either the NMES device or compression
117 stockings.

118 The geko™ NMES device was used for the study, which is small disposable and
119 internally powered and can be applied externally to the leg. The device is
120 manufactured by Firstkind Ltd., High Wycombe, United Kingdom. It is self-adhesive
121 and applied to the outer/posterior aspect of the knee. This positioning enables
122 integral electrodes to apply a stimulus to the lateral popliteal nerve (often additionally
123 termed the common peroneal) which branches from the sciatic nerve These nerves
124 control the contraction of several muscles in the lower leg. The stimulation of these
125 nerves by the geko™ device causes the muscles to contract isometrically and will
126 not affect normal movement of the limb nor mobility of the patient. Contraction of the
127 lower leg muscles increases blood flow from the lower limbs back to the heart thus
128 increasing venous return, local blood circulation and help prevent venous thrombosis
129 (Tucker et al. 2010). Saphena® anti-embolism compression stockings fitted in
130 accordance to manufacturer instructions were used for the study, with a pressure of
131 18 mmHg =/-20% administered to the ankle, 14mmHg +/- 20% administered to the
132 calf and 9mmHg +/- 20% to the thigh. Both devices were worn continually from post-
133 surgery until discharge. In accordance with the manufacturer's instructions for use,
134 the NMES device was changed each day.

135

136

137 Table 1 – Details of inclusion and exclusion criteria

Inclusion Criteria
• Aged 18 years of age and over • Free of significant abnormal findings as determined by medical history. • Has not used any medications (prescribed or over-the-counter including herbal remedies) judged to be significant by the Principal Investigator during the ten (10) days preceding enrolment. • Able to understand the Patient Information Sheet and willing to sign the written Informed Consent Form. • Able and willing to follow the protocol requirements.
Exclusion Criteria
• Are requiring hip revision surgery • History or signs of previous deep or superficial vein thrombosis/pulmonary embolism. • Evidence of asymptomatic DVT by Duplex Ultrasound • Peripheral arterial disease (ABPI < 0.8), varicose veins or lower limb ulceration or ischemia. • Significant varicose veins, phlebitis or lower limb ulceration or ischemia. CEAP Grade 4-6. See Appendix 2 • Recent surgery within the last 3 months (such as abdominal, gynaecological, hip or knee replacement). • Recent trauma to lower limb. • Chronic Obesity (BMI Index >40kg/m2). • Pregnancy. • Significant history of following diseases • Cardiovascular: Recent MI (< 6 months) • Percutaneous Coronary Intervention (PCI) with stent (< 3 months for Bare Metal

Stent (BMS) and < 12 months for Drug Eluding Stent (DES)

- Moderate to severe CCF, uncontrolled AF
- Neurological: Stroke, Hemiplegia/Paraplegia, Myopathies
- Significant dermatological conditions affecting lower limbs resulting in broken or inflamed skin particularly at the site where the device is to be fitted.
- Clinically significant haematological conditions i.e. coagulation disorders, sickle cell disease
- Psychiatric disorders
    - On LMWH/Heparin (Prophylactic/therapeutic doses) or Warfarin or warfarin stopped recently and replaced by LMWH/ Heparin
    - Long term steroid with dermatological changes
    - A pulse rate of less than 40 beats/minute
    - A sitting systolic blood pressure >180 and <100 mmHg and/or a sitting diastolic pressure of >100 mmHg.
    - Any significant illness during the four (4) weeks preceding the hip replacement surgery.
- Participation in any clinical study during the eight (8) weeks preceding the screening period

Data collection

Data were collected prior to surgery, immediately following surgery, on each post-operative day until discharge, and at 6 weeks following surgery. At each time point adverse events and device deficiencies were monitored.

Oedema was examined by taking measures of the circumference of the ankle, knee and thigh on the operated leg and non-operated leg, in the supine position, pre-operatively, post-operatively (prior to fitting of either the NMES or compression stocking devices), at two days post-operatively and every day until discharge (typically day four in this study population). The position the measurement was taken was marked with an indelible marker to ensure that measurements were always recorded on the same part of the ankle/leg, and the same staff member completed all measurements.

In addition to oedema evaluation, Duplex Ultrasound was used to assess the presence or absence of asymptomatic DVT in order to ensure the use of NMES over compression stocking did not increase DVT risk. All scans were completed by a consultant radiologist who examined the common femoral vein, superficial femoral vein, popliteal vein, gastrocnemius veins, soleal veins, posterior tibial veins and peroneal veins for patency, compressibility and the presence or absence of flow.

Evaluation of the acceptance and tolerability of both compression stockings and the NMES device was completed by the administration of a Likert Scale questionnaire designed to assess the level of pain/discomfort felt by the patient on a scale of 1-5.

Statistical Methodology

This feasibility study was deemed a necessary first step for the calculation of a suitable sample size for a future comprehensive study due to the shortage of existing suitable data for effect size. Incidence rates for oedema vary widely between patient groups and clinical settings, and the effect size for the NMES device for reducing the incidence of oedema was as yet unknown. .

For oedema data, graphs were plotted of circumference versus time and the gradients compared using a t-test. The frequency of asymptomatic DVT was recorded for each group at 0hrs (baseline scan) 48hrs post-operatively, discharge and Week 6. Rates of DVT (asymptomatic or symptomatic) were compared at each time-point, as well as the differences between time-points. Tolerability data for each intervention was collected on discharge, and measured using a Likert 1-5 scale. Interventions were subsequently compared with Mann-Whitney U-test. Additionally, safety was assessed for each intervention by the recording of adverse events. Additional data collected such as basic demographic information were checked by student's t-test to determine any differences between groups.

RESULTS

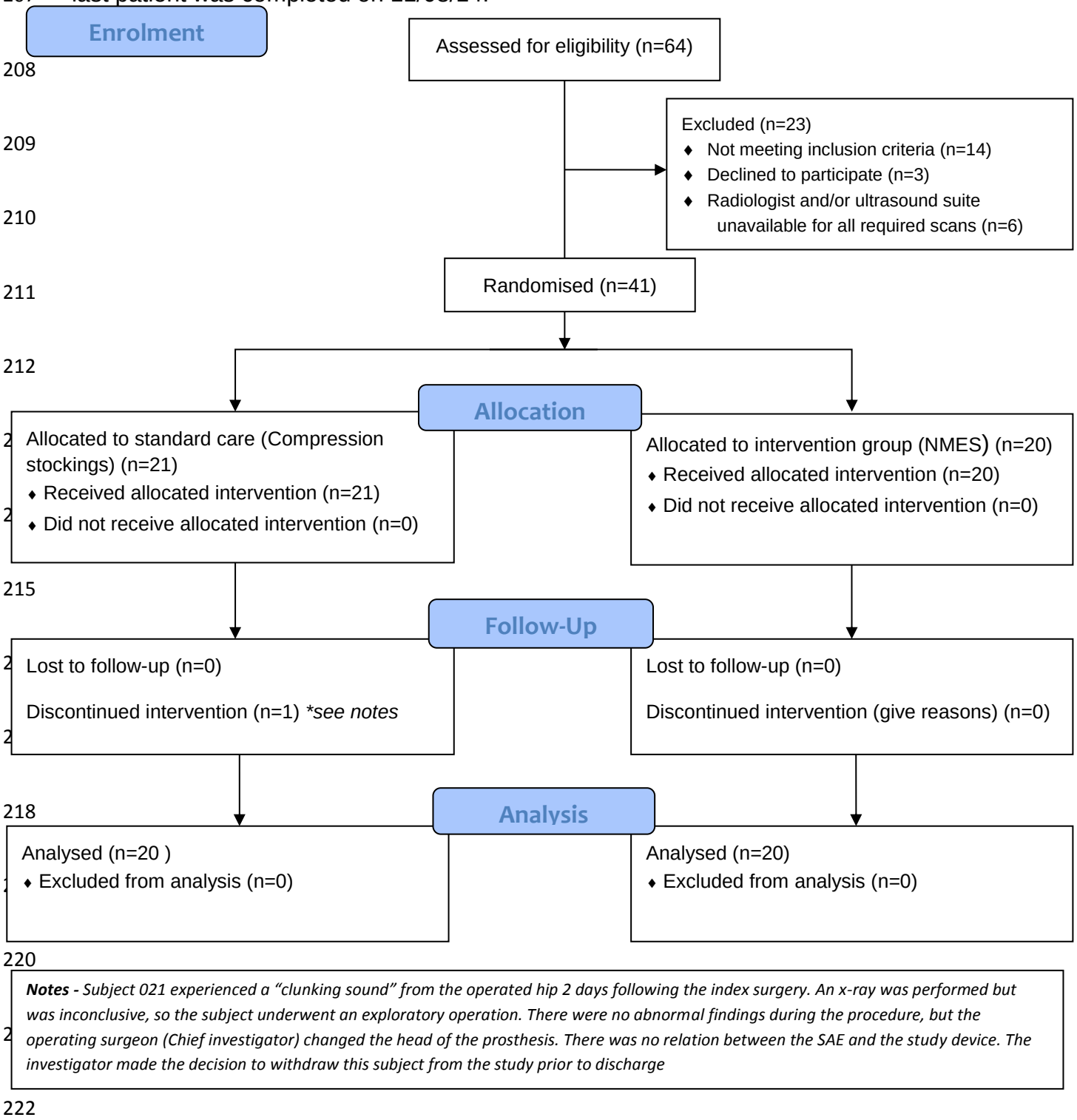
Successive patients were recruited between 28/08/13 and 09/07/14 until 40 patients had completed the trial, and follow up of the last patient was completed on 11/08/14. Forty-one patients scheduled for elective total hip replacement were enrolled into the study; one subject (021) was withdrawn due to withdrawal of consent as a result of an adverse event (See Figure 1). In general both study groups were well matched. A greater proportion of males were in the compression stockings group. The side operated on was more evenly distributed in the compression stockings population, whilst the right side received surgery in 70% of the NMES participants (See Table 2).

Table 2 – Baseline demographic and clinical characteristics

	NMES **Mean ± 95% CI**	**Compression Stockings** **Mean ± 95% CI**	**T-test or *Fishers exact p value**
Age (years)	67.2 ± 9.2	67.8 ± 11.9	0.87
Sex	14 Female/6 Male	5 Female/15 Male	*0.01
BMI (kg/m^2)	27.2 ± 4.3	26.5 ± 2.7	0.56
Treated leg	6 left, 14 right	8 left, 12 right	*0.74

Figure 1 - Participant flow diagram

Successive patients undergoing primary THR at the hospital were recruited between 28/08/13 and 09/07/2014 until 40 patients had completed the trial. Follow up of the last patient was completed on 11/08/14.

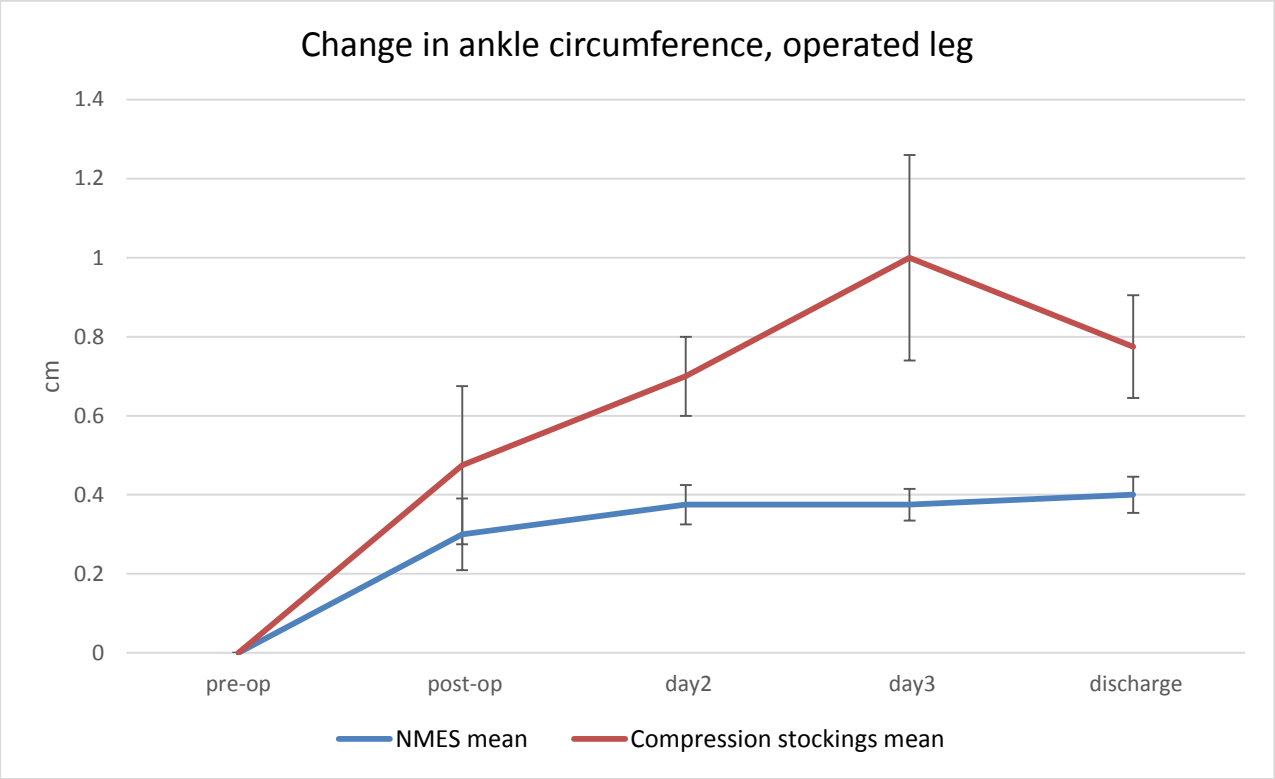


Oedema

There were no significant differences seen between the pre-operative swelling measured before the applications of the NMES device or compression stockings at the ankle (P=0.3), knee (P=0.12) or thigh (P=0.73) in the operated leg. Furthermore there were no significant differences seen between the post-operative swelling measured before the applications of the NMES device or compression stockings, at the ankle (P=0.5), knee (P=0.11) or thigh (P=0.44) in the non-operated leg.

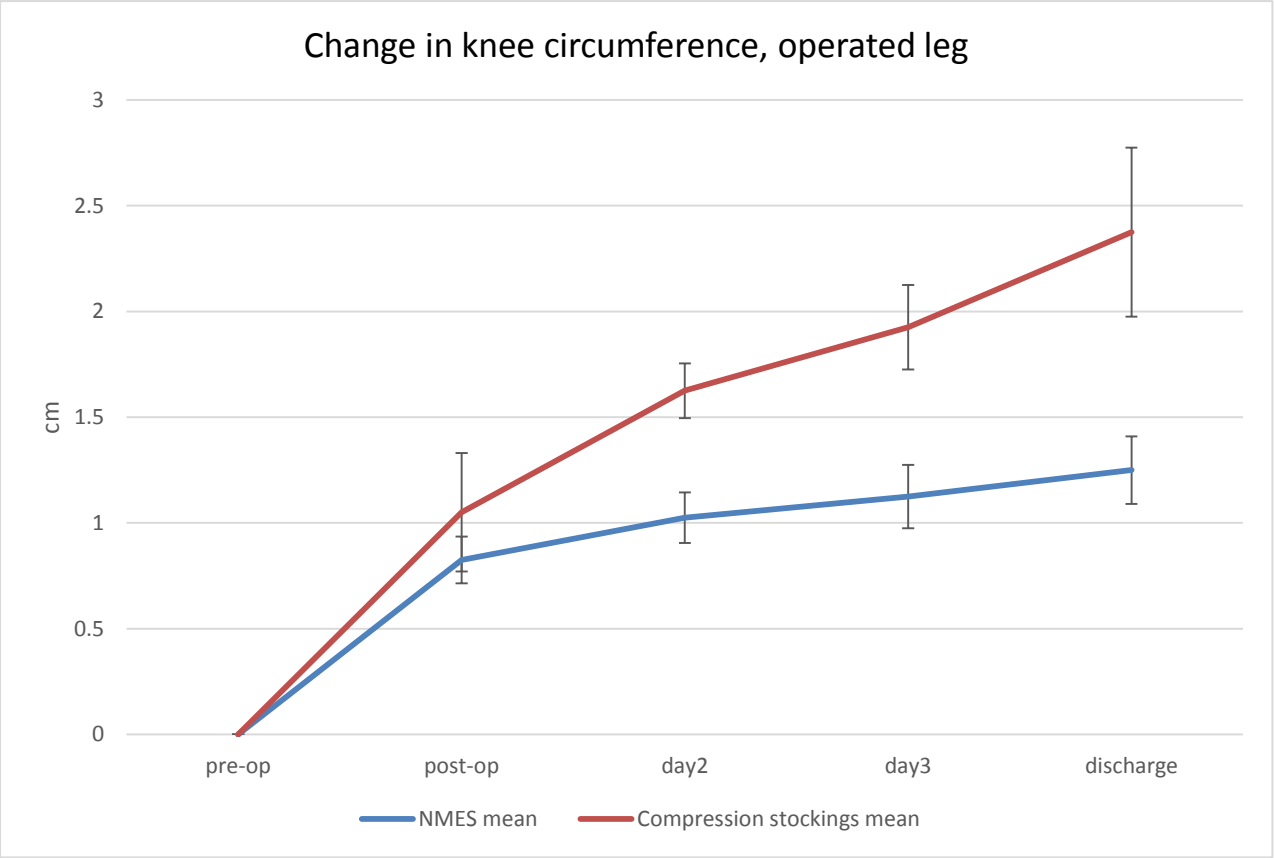
Figure 2 shows the mean ankle circumference during the post-op period to discharge relative to pre-op value for the NMES and compression stockings groups. Both groups exhibited an increase in this parameter, relating to ankle swelling during the post-op period, after application of the device. The compression stocking group ankle circumference increased by 0.48 cm ± 0.2 cm between pre-operative and post-operative measurements, the circumference peaked at day 3 (1 cm ± 0.4 cm) before dropping to 0.8 cm ± 0.3 cm on the day of discharge. The NMES group also saw an increase between the pre-operative measurements of ankle circumference and the post-operative measure prior to the device being fitted (0.3 cm ± 0.1 cm). The NMES group ankle circumference peaked on the day of discharge at 0.4cm±0.1. The compression stockings group ankle circumference increased more than the NMES group though this did not reach significance (p=0.27).

Figure 2 - Ankle circumference in the operated leg



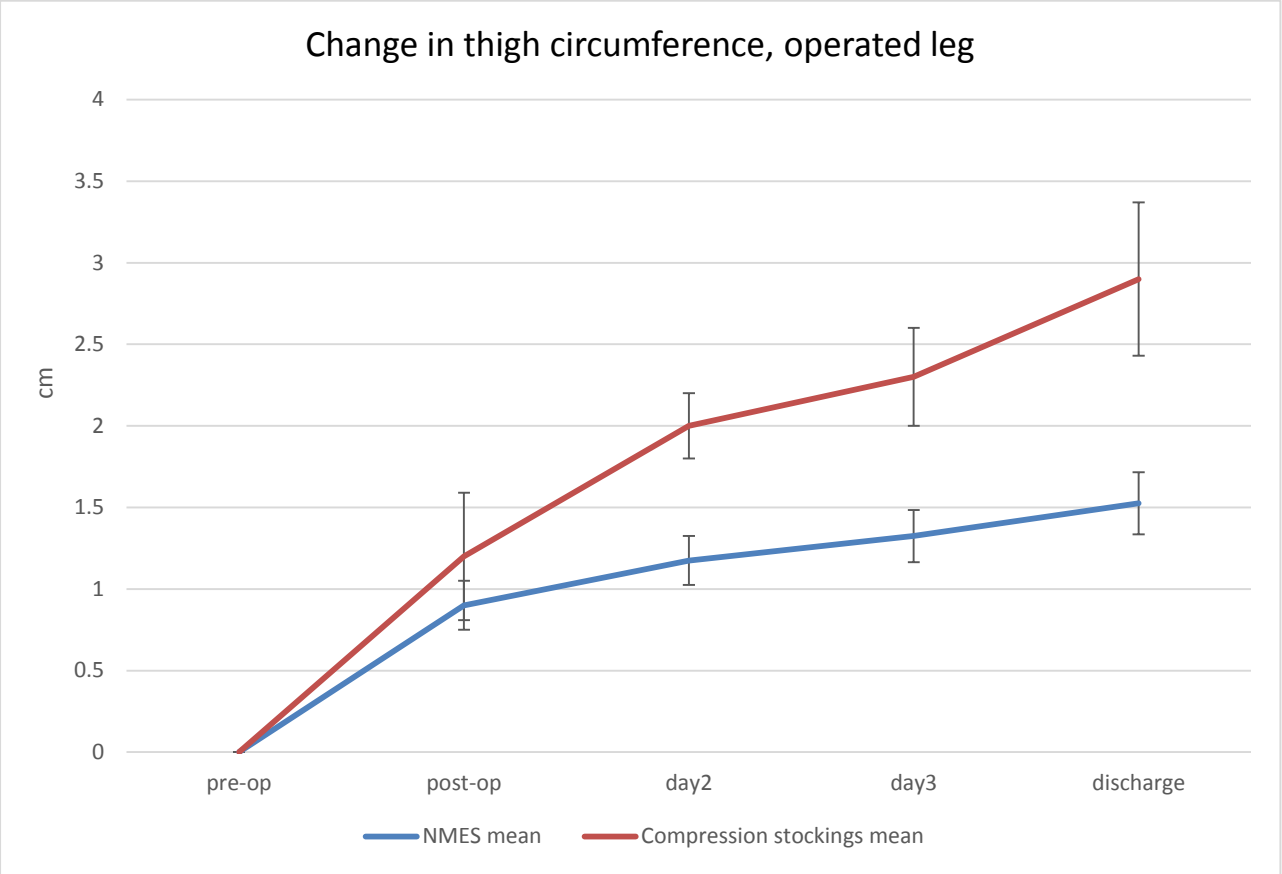
Similar results were seen for knee circumference (Figure 3). Both groups show an increase between pre-operative and post-operative measures before device fitting (NMES 0.8 cm ± 0.1 cm, compression stockings 1.1cm±0.3) which continued through to discharge (NMES 1.3 cm ± 0.2 cm, compression stockings 2.4 cm ± 0.5 cm), but in this case, the increase for the NMES group was significantly smaller than for the compression stockings group (p=0.02).

Figure 3 - Knee circumference in the operated leg



Similar results were seen for the thigh measurements as shown in Figure 4. Both NMES and compression stockings groups displayed significant increases in thigh circumference between pre-operative and post-operative measures prior to fitting the devices (0.9 cm ± 0.2 cm [p=0.004] and 1.2 cm ± 0.4 cm [p=0.002]). The circumference was highest in both NMES and compression stockings groups on the day of discharge (1.5 cm ± 0.3 cm and 2.9 ± 0.6 cm respectively. A significantly smaller increase in thigh diameter pre-op to discharge for the NMES group (1.5 cm ± 0.3 cm) as compared to the compression stockings group (2.9 cm ± 0.6 cm [p=0.02]) was observed.

Figure 4 - Thigh circumference in the operated leg



The treatment devices were worn on both legs by all study subjects. In the non-operated leg, no significant changes were seen in ankle circumference from immediate post-op to discharge for either group.

At the knee, the NMES group showed a non-significant decrease (p=0.19) in non-operated knee circumference immediately post-op (0.33 cm ± 0.1 cm) to discharge (0.25 cm ± 0.1 cm), while the compression stockings group showed a non-significant increase (0.23 cm ± 0.2 cm immediately post-op to 0.43 cm ± 0.2 cm [p=0.057]). The difference between the NMES and compression stockings groups on this parameter was significant (p=0.016) at discharge.

Similarly, at the thigh, the NMES group showed a non-significant decrease (p=0.095) in thigh circumference of the non-operated leg (post-operative 0.55 cm ± 0.2 cm to 0.1 cm ± 0.3 cm on the day of discharge). However, the compression stockings group showed a significant (p=0.021) increase in thigh circumference of the non-operated leg after application post-op (0.38 cm ± 0.3 cm) to discharge (0.75 cm ± 0.3 cm). The difference between the NMES and compression stockings groups was highly significant (p=0.006) at discharge.

Incidence of symptomatic or asymptomatic DVT

There were no symptomatic or asymptomatic DVTs observed via ultrasound occurring at any time point up until 6 weeks in either the NMES or compression stockings groups. There were no VTE, PE, stroke or deaths recorded during the study in either NMES or compression stockings treatment groups.

Patient rated outcome measures

Participants were asked at the end of their hospital stay the following question "*When compared to a blood pressure cuff inflated around your upper arm, how does the device/stocking feel?*" in order to gain an understanding as to their tolerance of the device. Over 80% of all participants i.e those randomised to NMES and compression stockings reported minimal or no sensation from their devices. There were n=5 compression stockings participants who reported either mild or severe discomfort caused by their devices, compared with only n=2 NMES participants reporting the same, this however did not reach significance (Fisher Exact Test, P=0.28), see table 3 below

Table 3 - Patient reported comfort

How does the device feel	Group		
	NMES	**Compression stockings**	**Total**
1= No sensation	1 (2.5%)	4 (10%)	5 (12.5%)
2= Minimal sensations	16 (40%)	12 (30%)	28 (70%)
3= Mild discomfort	2 (5%)	4 (10%)	6 (15%)
4= Moderate discomfort	0 (0%0	0 (0%)	0 (0%)
5= Severe discomfort	0 (0%)	1 (2.5%)	1 (2.5%)

Adverse events

A total of 19 adverse events (AEs) were reported during the study. The majority of these were post-operative pain (n=12, 63.2%). None had causality related to the device. From these 19 adverse events, 4 were classified as serious adverse events (SAEs). None of the SAEs were considered Unanticipated Serious Adverse Device Effects (USADEs). No device deficiencies were reported throughout the duration of the study.

DISCUSSION

This feasibility study was set up to provide data to adequately power a larger, multi-centre study. As such, the statistical powering and sample size of 40 participants was not designed to identify differences in oedema or DVT incidence between the interventions. Whilst the sample size is small, the fact that this was a single surgeon series, within the same hospital means that a high degree of pathway and treatment standardisation was possible. This is an important factor when assessing outcomes such as oedema or DVT which may have multi-factorial contributing factors.

The NMES device provided a potentially highly significant clinical benefit of helping to limit the amount of post-operative oedema. The NMES device performed significantly better than compression stockings in treating post-operative oedema of the knee and thigh that occurs following THR in both the operated and non-operated legs. It is acknowledged that the measurement technique for oedema evaluation has limitations, but given the circumference changes reported, and the steps to ensure reliability (same assessor and marked points of measurement), it is highly likely the differences reported are real. Any future studies, most seek to confirm these oedema findings, and aim to establish the clinical significance of reduced oedema, by linking to functional outcomes such as muscle function and functional ability.

In addition, the data provides extremely encouraging data and support for the use of the geko^{TM} device which is a new and novel form of NMES. This is because there were no AEs or SAEs attributable to the NMES device and no device deficiencies were reported. In addition, all participants were able to tolerate wearing the NMES devices continuously for the duration of their post-operative recovery in hospital 24

hours per day. These results suggest that the NMES device is both safe and robust enough to use in the clinical setting.

The positive patient tolerability data for the NMES device is especially interesting given that patient compliance with compression stockings has been previously reported to be low owing to issues of discomfort, difficulty applying and appearance. In addition, the use of compression stockings is contra-indicated in patients with leg oedema, cardiac failure, peripheral vascular insufficiency, and venous ulceration, which can limit their applicability, particularly in elderly populations who frequently have hip replacements procedures. Indeed, for patients where mechanical/pharmacological methods of prophylaxis are impractical or contraindicated, NICE medical technologies guidance recommend the adoption of NMES (Summers et al. 2015) and this study further supports the NICE position. Incorrectly fitted compression stockings have also been associated with ischemia and increased risk of DVT and a recent study has found a significant increase in skin problems, including breaks, ulcers, blisters, and necrosis in patients who were fitted with compression stockings. Future work will need to consider the cost of compression stockings compared to the NMES device given the current economic challenges within the National Health Service (NHS). It is acknowledged that compression stockings may be cheaper to purchase, however health economists should consider the overall patient cost in regards to readmissions, complications and additional rehabilitation needs.

Finally, length of stay (LOS) was not used as an outcome measure within this study as all participants stayed in hospital for four days due to funding arrangements for

patient care used within the hospital. However, using NMES to reduce the formation of post-operative oedema may have a positive effect on LOS. The relationship between reduced oedema and improvement to muscle strength has not yet been proven. However we theorise that reducing oedema will encourage mobilisation and thus improve muscular strength and achievement of discharge criteria and early functional recovery.

CONCLUSION

Recent studies on fast-track (or Enhanced Recovery after Surgery) cohorts suggest that there may be an increased role for non-pharmalogical devices that can be used whilst walking (Jorgensen & Kehlet 2017). This is the first randomised controlled trial to evaluate the effectiveness of the geko^{TM} device. The results of this study suggest that the NMES device is safe, well tolerated by patients and may be more effective than compression stockings in reducing the formation of post-operative oedema. In addition and in respect to DVT prophylaxis, our findings suggest that the NMES device could be used as adjunctive to chemoprophylaxis or, as recommended by NICE, as a standalone intervention when other methods are impractical or contraindicated.

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