Check for updates

Review Article

Phlebology

Phlebology
2018, Vol. 33(6) 367–378
© The Author(s) 2017
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0268355517710130
journals.sagepub.com/home/phl
SAGE

Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Raveena Ravikumar, Katherine J Williams, Adarsh Babber, Hayley M Moore, Tristan RA Lane, Joseph Shalhoub and Alun H Davies

Abstract

Objective: Venous thromboembolism, encompassing deep vein thrombosis and pulmonary embolism, is a significant cause of morbidity and mortality, affecting one in 1000 adults per year. Neuromuscular electrical stimulation is the transcutaneous application of electrical impulses to elicit muscle contraction, preventing venous stasis. This review aims to investigate the evidence underlying the use of neuromuscular electrical stimulation in thromboprophylaxis.

Methods: The Medline and Embase databases were systematically searched, adhering to PRISMA guidelines, for articles relating to electrical stimulation and thromboprophylaxis. Articles were screened according to a priori inclusion and exclusion criteria.

Results: The search strategy identified 10 randomised controlled trials, which were used in three separate meta-analyses: five trials compared neuromuscular electrical stimulation to control, favouring neuromuscular electrical stimulation (odds ratio of deep vein thrombosis 0.29, 95% confidence interval 0.13–0.65; P = .003); three trials compared neuromuscular electrical stimulation to heparin, favouring heparin (odds ratio of deep vein thrombosis 2.00, 95% confidence interval 1.13–3.52; P = .02); three trials compared neuromuscular electrical stimulation as an adjunct to heparin versus heparin only, demonstrating no significant difference (odds ratio of deep vein thrombosis 0.33, 95% confidence interval 0.10–1.14; P = .08).

Conclusion: Neuromuscular electrical stimulation significantly reduces the risk of deep vein thrombosis compared to no prophylaxis. It is inferior to heparin in preventing deep vein thrombosis and there is no evidence for its use as an adjunct to heparin.

Keywords

Venous thromboembolism prophylaxis, deep vein thrombosis

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of morbidity and mortality. It affects one in 1000 adults per annum[1] and is responsible for 25,000 preventable hospital-related deaths,[2] making it the single most common cause of hospital-related mortality in the United Kingdom. DVT is associated with significant long-term morbidity due to recurrence, venous hypertension and post-thrombotic syndrome (PTS). PTS affects up to 50% of patients with proximal DVT[3] and leads to venous ulceration in 5–10% of cases. The overall cost of treating VTE in the United Kingdom is estimated to be £640 million.[2]

VTE prophylaxis methods aim to combat venous stasis, hypercoagulability and endothelial injury: the three factors predisposing to venous thrombosis.[4] Pharmacological agents such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) and new oral anticoagulants (NOACs) prevent the development and propagation of clots. Mechanical devices

Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London, Charing Cross Hospital, London, UK

Corresponding author:
Alun H Davies, Room 4E04, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK.
Email: a.h.davies@imperial.ac.uk

such as graduated compression stockings (GCSs) and intermittent pneumatic compression (IPC) act via passive mechanisms to prevent venous stasis by applying graded circumferential pressure distally to proximally[5] and increasing venous flow,[6] respectively.

The combination of pharmacological and mechanical thromboprophylaxis has been shown to significantly reduce the relative risk of DVT.[7] National guidelines recommend the use of mechanical agents such as elastic stockings and IPC in VTE prophylaxis.[8,9] However, limitations of IPC include improper fitting, inappropriate use of device, peroneal nerve injury, discomfort and excessive heating under the inflatable cuffs.[10] Elastic stockings are associated with poor compliance and complications such as skin breaks, ulcers and blisters.[11]

Neuromuscular electrical stimulation (NMES) is the application of electrical impulses via transcutaneous electrodes to elicit muscle contraction either directly to the muscle belly itself or indirectly via a nerve supplying a muscle group. Activation of lower limb muscle pumps with NMES has been shown to increase venous time-averaged mean velocity, peak venous velocity and volume flow (VF) comparable[12,13] or superior[14,15] to IPC.

The role of NMES in venous thromboprophylaxis has been investigated since the 1960s but did not gain popularity due to antiquated technology which only permitted its use in anaesthetised patients.[16] In addition, the widespread use of LMWH and mechanical devices such as GCS and IPC in clinical practice led to a loss of interest in this technology.

Recently, the UK National Institute for Health and Care Excellence (NICE) issued a medical technology guidance (NICE MTG19) permitting the use of the geko™, a new and portable NMES device in patients who are not suitable for other modes of prophylaxis.[17] This review aims to investigate the evidence underlying the use of NMES in thromboprophylaxis.

Methods

Search strategy

The Medline and Embase databases were systematically searched on 15 February 2016, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[18] guidelines to identify relevant articles. The keywords used in the search string were 'deep vein thrombosis' OR 'deep venous thrombosis' OR 'DVT' OR 'venous thromboembolism' OR 'VTE' AND 'electric$' AND 'stimulation' (Appendix 1). Human studies and English language limitations were applied. Duplicates were removed from the search. The search was augmented by manually reviewing the cited references.

Study selection

Randomised controlled trials (RCTs) assessing the application of electrical stimulation to elicit muscle contraction in surgical and non-surgical patient groups were eligible for inclusion.

The primary outcome measure was the incidence of DVT. Only imaging-proven DVTs were included in the analysis. Imaging modalities included radiolabelled iodine fibrinogen uptake test (^{125}I-FUT), venography, Doppler ultrasound, computed tomography venography or magnetic resonance venography.

The secondary outcome measure was the incidence of PE. Only imaging-proven diagnosis of PE using either ventilation–perfusion scan or computed tomography pulmonary angiography (CTPA) was included in the analysis.

The analysis aimed to assess the odds ratio (OR) of developing DVT and PE with NMES compared to no prophylaxis and other methods of thromboprophylaxis including compression stockings, IPC, heparin, LMWH and NOACs. Subgroup analysis comparing DVT risk reduction between surgical and medical patient groups was to be performed. Cost-effectiveness analysis of NMES compared to other modalities of thromboprophylaxis would be performed to assess the cost–benefit of this treatment.

Titles and abstracts identified were screened and full text articles independently assessed according to the a priori agreed eligibility criteria stated above by two reviewers (RR and KW).

Data extraction and quality appraisal

Data extraction and assessment of methodological quality were performed independently by the same authors (RR and KW). Any discrepancy was adjudicated by the senior author (AHD). Data were extracted on study details (e.g. author, year), patient population (e.g. demographics and type of surgery), details of interventions (e.g. comparators in each arm of RCT, device data, whether device was used intraoperatively or postoperatively) and details of outcome measure (imaging modality, day imaging performed postoperatively) and duration of follow-up.

Quality assessment

The quality of individual RCTs was assessed using the Cochrane Collaboration risk of bias assessment tool (Review Manager 5.3)[19] by two authors (RR and KW), independently. Disagreements were

adjudicated by a third reviewer (AB). The risk of bias tool consists of seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each domain was graded as high, low or unclear. An overall risk of bias was assigned for each trial; high overall risk of bias for trials in which one or more domains were considered high risk, low overall risk of bias if all key domains were judged to have low risk of bias and unclear risk of bias if one or more domains were judged to have an unclear risk of bias.

Statistical analysis

The meta-analysis was conducted as part of the quantitative analysis using the Review Manager 5.3 software.[19] The OR of DVT for each comparison group was calculated using a random effects model, using the Mantel–Haenszel statistical method. The I^2 statistic was employed to quantify the statistical heterogeneity. Data on the incidence of PE related to the use of NMES were tabulated and synthesised narratively.

Results

The search strategy returned 151 articles. Additional records were identified by manually reviewing cited references. Forty-one full text articles were identified following screening of titles and abstracts. Ten RCTs provided data on imaging-proven DVT and were included for quantitative analysis. The PRISMA flow chart for the search strategy is shown in Figure 1.

Quantitative analysis

In general, reporting of trial methodology was poor. Description of blinding, randomisation technique and allocation concealment were missing in most trials. Randomisation techniques utilised pre-drawn up list,[20,21] date of birth,[22,23] alternate patient,[24] sealed envelope,[6,25] randomisation table[26] or computer generated.[27]

There was substantial clinical variation between the 10 trials with respect to the patient population: general surgical,[6,20,21,23,28] neurosurgical,[22] orthopaedic,[25] trauma[24,27] and non-surgical patients[26] were included. In the surgical trials, NMES was used either intraoperatively[6,20–25,28] or postoperatively.[27] The trials

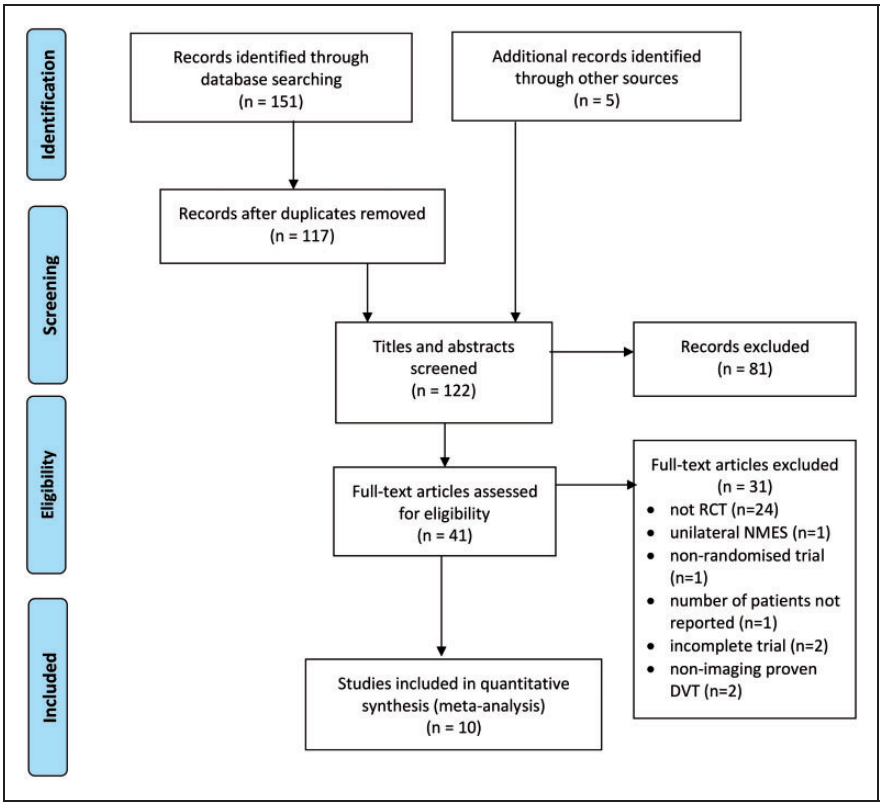

Figure 1. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart demonstration stages of meta-analysis.

Table 1. Characteristics of trials included in meta-analysis comparing NMES to pure controls who did not receive any thromboprophylaxis.

Author (year)	Patient population	Intervention	Control	Duration NMES	VTE diagnostic criteria	Outcome of DVT	Follow up	Overall risk of bias
Nicolaides et al. (1972)[28]	General surgery (n = 116) VTE risk factors (Intervention versus control): age 52y versus 56y, obesity 27% versus 21%, previous VTE 8% versus 7%, malignancy 18% versus 25%.	Unilateral NMES (n = 60)	No thrombo Prophylaxis (n = 56)	Intraoperative	^{125}I-FUT Preop day 1, 3, 5, 7, 9 postop	NMES 1 limb (1.6%) Control 25 limbs (32.1%)	10 days	Unclear
Becker and Schampi (1973)[21]	General surgery (n = 116) VTE risk factors (Intervention versus control): age 64y versus 66y	Bilateral NMES (n = 39)	No thrombo prophylaxis (n = 35)	Intraoperative	^{125}I-FUT preop postop Phlebography (if + ve ^{125}I-FUT)	NMES 2 patients (5.1%) Control 11 patients (31.4%)	11 days	High risk
Rosenberg et al. (1975)[23]	General surgery (n = 194) VTE risk factors not described	Bilateral NMES (n = 73)	No thrombo prophylaxis (121)	Intraoperative	^{125}I-FUT preop -day 1, 3, 5, 7 postop	NMES 22 patients (30.1%) Control 50 patients (41.3%)	7 days	High risk
Lindstorm et al. (1982)[20]	General surgery (n = 112) VTE risk factors (intervention versus control): age 63.7y versus 66.5y, previous VTE 0% versus 2.5%, malignancy 35% versus 33%.	Bilateral NMES (n = 37)	No thrombo prophylaxis (n = 40)	Intraoperative	DVT ^{125}I-FUT - alternate days (max day 4–6) Phlebography (if + ve ^{125}I-FUT)	NMES 5 patients (13.5%) Control 12 patients (30%)	6 days	High risk
Goyal et al. (2012)[24]	Hip fracture surgery (n = 200) VTE risk factors (intervention versus control): Age 55y versus 53y Similar operations between groups.	Bilateral NMES (n = 100)	No thrombo prophylaxis (n = 100)	Intraoperative	Ultrasound -preop -sonographer blinded	NMES 2 patients (2.0%) Control 6 patients (6.0%)	7 days	High risk

DVT: deep vein thrombosis; ^{125}I-FUT: ^{125}iodine labelled fibrinogen uptake test; NMES: neuromuscular electrical stimulation; postop: postoperative; preop: preoperative; VTE: venous thromboembolism; y: years.

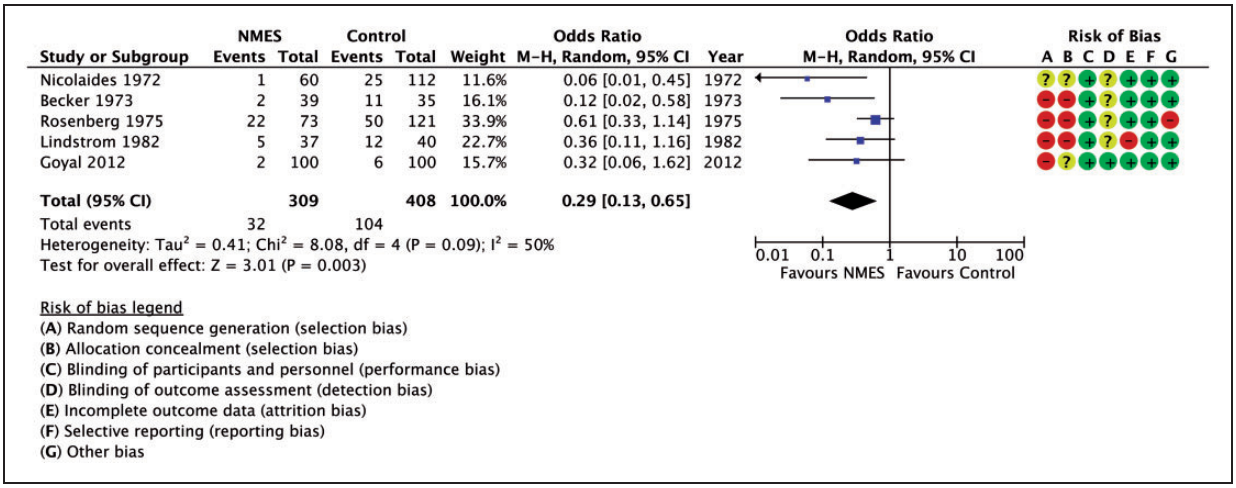

Figure 2. Forest plot showing the odds ratio of developing deep vein thrombosis (DVT) with neuromuscular electrical stimulation (NMES) compared to control (no thromboprophylaxis).

compared the incidence of DVT in patients receiving NMES to no prophylaxis,[20,21,23,24,28] heparin,[6,22] dextran,[20,21] IPC[6] and as an adjunct to standard therapy.[25–27] Standard therapy was variable in trials with both groups receiving either heparin + IPC[25,27] or heparin alone.[26]

The diagnosis of DVT was determined via ^{125}I-FUT,[6,20–23,26,28] impedance plethysmography,[26] phlebography[20,21,27] and ultrasound.[24,25,27] The protocols for ^{125}I-FUT were variable, with pretreatment ^{125}I-FUT performed in some studies,[6,21,28] but not others.[20,23] The diagnostic criteria and number of measurements per limb were also variable. Phlebography[20,21,26,27] was used to confirm the diagnosis, but this was not performed in all patients due to technical reasons, patient choice and the greater sensitivity of ^{125}I-FUT to detecting thrombi.

The follow-up duration of the study varied between one day postoperative[25] to 28 days[26] (median 10 days). DVT was most frequently detected in the first postoperative day (53.2%), decreasing to 27.7 and 18.9% over the first 72 h and nine days, respectively.

The variation in devices, electrical parameters and electrode placement is detailed in supplemental Table 1. Reporting of electrical parameters was not standardised, precluding any meaningful comparison between the devices. Older trials utilised galvanic (direct) current, whereas newer devices used alternating current. Despite the variation in NMES devices, the underlying principle of all the devices was an increase in venous haemodynamics to prevent venous stasis. This was demonstrated in both the older trials that reported an increase in blood flow of up to 3.8-fold with intraoperative NMES[21,28] and newer trials that reported an increase in VF and peak velocity of up to 2.7- and 3.9-fold, respectively.[15] Therefore, despite device heterogeneity, calf pump output was similar across different techniques.

DVT results

Three meta-analyses were performed comparing:

(a) NMES versus controls (no thromboprophylaxis)
(b) NMES versus heparin
(c) NMES as an adjunct to heparin compared to heparin alone (NMES + heparin versus heparin alone).

NMES versus control

Five RCTs compared the effect of NMES to pure controls (no thromboprophylaxis). Trials involved general surgical patients[20,21,23,28] and trauma patients with hip fractures undergoing surgery under spinal anaesthetic.[24] Patients in the NMES and control group had comparable VTE risk factors (Table 1). Trial methodology was weak, but sample sizes were large. Randomisation techniques used either month of birth,[23] alternated patients to groups[24] or were not described.[20,21] As NMES was only administered intraoperatively, this was considered blinding of participant and personnel.

A total of 717 patients were included in the analysis: 309 in the NMES group and 408 in the control group. The imbalance in groups is attributed to two factors: the control group for the trial by Nicolaides et al.[28] was reported as number of limbs affected (56 patients, 112 limbs) as the intervention group received unilateral NMES, and the method of randomisation by

Table 2. Characteristics of trials included in meta-analysis comparing NMES to unfractionated heparin.

Author (year)	Patient population	Intervention	Comparator	Duration NMES	VTE diagnostic criteria	Outcome	Follow up	Overall risk of bias
Rosenberg et al. (1975)[23]	General surgery (n = 194) VTE risk factors not described	Bilateral NMES (n = 73)	Control (121) UFH[a] (n = 79)	Intraoperative	^{125}I-FUT - preop - day 1, 3, 5, 7 postop	NMES 22 patients (30.1%) UFH 12 patients (15.2%)	7 days	High risk
Nicolaides et al. (1983)[6]	General surgery (n = 150) VTE risk factors (NMES versus heparin): age 39.2y versus 58.6y previous VTE 4% versus 4% malignancy 36 and versus 38%	Bilateral NMES (n = 50)	UFH[b] (n = 50)	Intraoperative	^{125}I-FUT - preop - alternate days postop	NMES 12 patients (24%) UFH 7 patients (14%)	N/A	High risk
Bostrom et al. (1986)[22]	Neurosurgical patients (n = 89) VTE risk factors (NMES versus heparin):Age 59y versus 60y Weight 71 kg versus 74 kg Duration of operation 3.4 h versus 3.1 h	Bilateral NMES + postop dextran (n = 40)	UFH[b] (n = 49)	Intraoperative	^{125}I-FUT - day 5–8 postop. Phlebography (if + ve ^{125}I-FUT)	NMES 5 patients (13%) UFH 5 patients (10%)	7 days	High risk

DVT: deep vein thrombosis; ^{125}I-FUT: ^{125}iodine labelled fibrinogen uptake test; N/A: not available; NMES: neuromuscular electrical stimulation; postop: postoperative; preop: preoperative; UFH: unfractionated heparin; VTE: venous thromboembolism; y: years.

[a]5000 iu 8°.

[b]5000 iu BD.

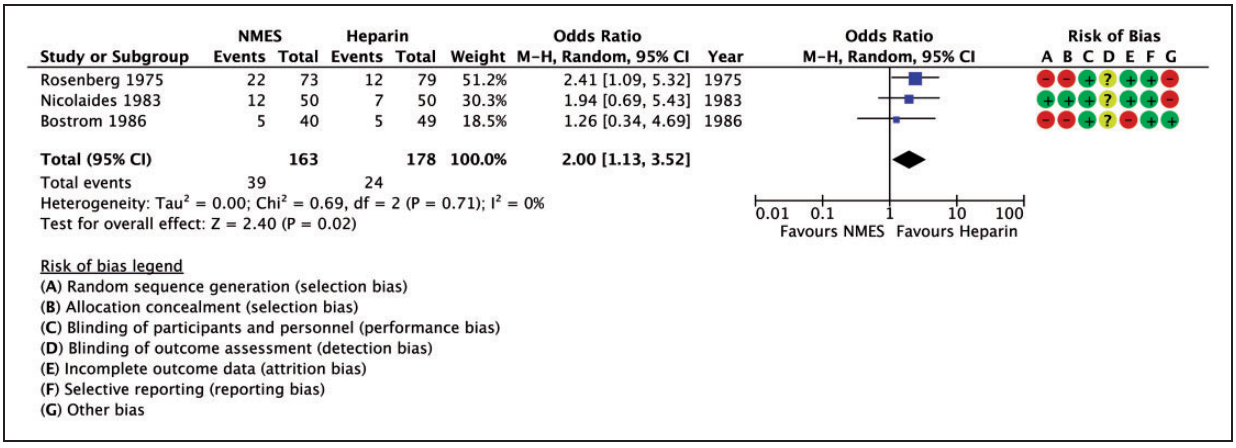

Figure 3. Forest plot showing the odds ratio of developing deep venous thrombosis (DVT) with neuromuscular electrical stimulation (NMES) compared to unfractionated heparin.

Rosenberg et al.[23] was by month of birth, leading to poorly matched groups.

The pooled incidence of DVT in the NMES group (10.4%) was significantly lower than the control group (25.5%), with a corresponding OR of 0.29 (95% confidence interval (CI) 0.13–0.65; P = .003; Figure 2). However, there was no statistically significant heterogeneity across the trials ($I^2 = 50\%$; P = .09).

NMES versus heparin

Three RCTs compared the effect of NMES to UFH (5000 iu BD), with 163 patients in the NMES group and 178 patients in the heparin group.[6,22,23] Trials involved general[6,23] and neurosurgical patients.[22] Two trials were comparable in terms of VTE risk factors (Table 2)[6,22] and the remaining trial did not provide this detail.[23] Once again, NMES was only administered intraoperatively and the quality of trials was a limiting factor due to randomisation techniques using the month[23] and date[22] of birth. Other sources of bias include failure to observe protocol[23] and patient exclusion following randomisation due to complications (reason given).[22]

The OR of developing DVT was significantly higher with NMES compared to UFH (NMES 23.9% versus UFH 13.4%; OR 2.00, 95% CI 1.13–3.52; P = .02) as shown in Figure 3. There was low statistical heterogeneity between these trials ($I^2 = 0\%$; P = .71).

NMES + heparin versus heparin alone

Three studies compared the effect of NMES as an adjunct to heparin to heparin only. Devices used in the trials were modern with no reported complications.[25–27] There was substantial clinical variability between trials including patient population (patients with acute spinal cord injury,[26] postoperative severe trauma surgery[27] and intraoperative NMES during total knee arthroplasty surgery[25]) and duration of follow-up (1–28 days) (Table 3). Trials used subcutaneous UFH only[26] or either UFH or LMWH.[25,27]

Prior power calculations (power 0.8, α 0.05) to predict the sample size for their respective patient populations were performed for two trials.[25,27] However, one trial was discontinued prematurely due to lack of funding and clinically important trends.[27] This was considered a risk for reporting bias.

The pooled group had 168 patients, 86 in the NMES + heparin group and 82 in the heparin only group. The OR of developing DVT was lower with combination therapy than with heparin alone, but this was not statistically significant (15.1% versus 34.1%; OR 0.33, 95%CI 0.10–1.14; P = .08; Figure 4). There was no statistically significant heterogeneity between the three trials ($I^2 = 53\%$; P = .12).

Incidence of PE

Lindstrom et al.[20] reported a 19% absolute risk reduction (ARR) of PE in general surgical patients receiving intraoperative NMES compared to no thromboprophylaxis (P < .05).

Comparing NMES with IPC

Nicolaides et al.[6] reported a significant reduction in the incidence of DVT with IPC (4% versus 18%; P < .0025) and UFH (9% versus 18%; P < .05) compared to NMES. However, the duration of thromboprophylaxis for each group varied; patients in the NMES group only received treatment intraoperatively, whereas the

Table 3. Characteristics of trials included in the meta-analysis comparing NMES as an adjunct to heparin versus heparin alone.

Author (year)	Patient population	Intervention	Comparator	Duration NMES	VTE diagnostic criteria	Outcome	Follow-up	Overall risk of bias
Merli et al. (1988)[26]	Acute (< 2/52) spinal cord injury (n = 48) VTE risk factors: Authors reported no statistically significant difference between groups in age, gender, medical history and admission date.	UFH[a] + NMES (n = 15)	UFH[a] (n = 16)	Non-surgical	^{125}I-FUT Phlebography (if + ve ^{125}I-FUT)	UFH + NMES 1 (6.7%) UFH 8 (50%)	28 days	High risk
Velmahos et al. (2005)[27]	Major trauma patients (ISS > 9) not suitable for heparin (n = 60) VTE risk factors (intervention versus comparator): Age 32y versus 45y (p < 0.01) BMI 27 versus 29 Injury Severity Score 20 versus 19	Bilateral NMES (n = 30) Heparin[b] ± IPC used when contraindications no longer present (3–5 days).	Control (n = 30)	Postoperative 2x 30 min ES/day for 7-14 days	Ultrasound preop at discretion of physician Bilateral venography - between day 7 and 15	Proximal DVT: NMES: 3 (11.5%) Control 3 (14.2%) DVT (total) NMES 7 (26.9%) Control 6 (28.5%)	14 days	High risk
Izumi et al. (2014)[25]	Total knee arthroplasty (TKA) (n = 90) VTE risk factors (intervention versus comparator): Age 76y versus 75y BMI 26.5 versus 26.6 Operation time 109 versus 118 min	NMES (n = 45) - NMES on operated limb, IPC/GCS on contralateral limb	Control (n = 45) - IPC and heparin[c] postop in both groups	Intraoperative NMES	DVT Ultrasound (postop day1)	NMES 11% Control 31%	1 day	High risk

DVT: deep vein thrombosis; GCS: graduated compression stockings; ^{125}I-FUT: ^{125}iodine labelled fibrinogen uptake test; IPC: intermittent pneumatic compression; ISS: injury severity score; NMES: neuromuscular electrical stimulation; UFH: unfractionated heparin; VTE: venous thromboembolism.

[a]5000 iu 8°.

[b]Unfractionated heparin/low molecular weight heparin.

[c]Fondaparinux or LMWH.

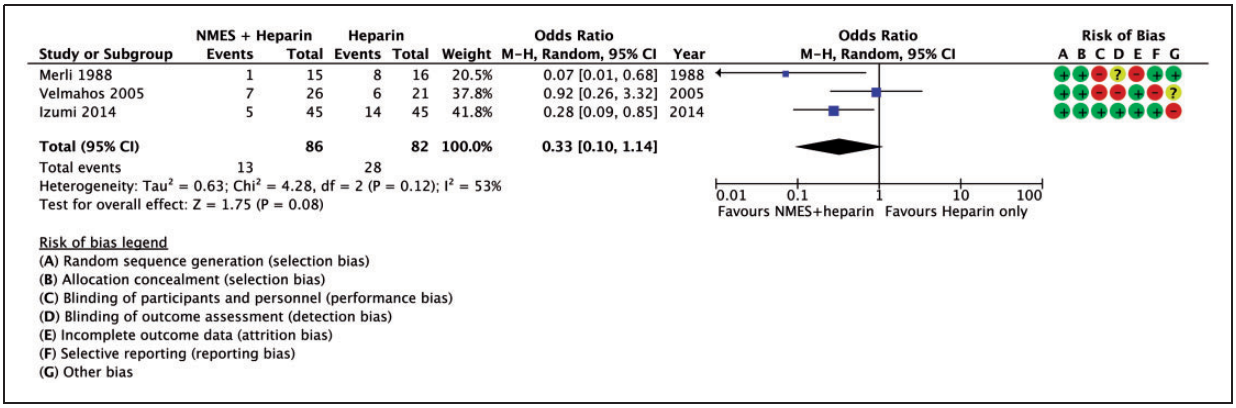

Figure 4. Forest plot showing the odds ratio of developing deep venous thrombosis (DVT) with neuromuscular electrical stimulation (NMES) compared to NMES in combination with heparin.

IPC group received treatment for a minimum of 72 h or until ambulant.

Comparing benign and malignant disease

Rosenberg et al. compared the effect of NMES in benign and malignant disease, reporting that whilst both NMES and UFH reduced the incidence of DVT in benign disease (ARR 18.9 and 26.3%; $P < .01$ and $P < .001$, respectively), only UFH reduced the incidence of DVT significantly in malignant disease (ARR 54.6%; $P < .001$).

Discussion

The results of the meta-analyses show that NMES significantly reduces the odds of developing DVT compared to no thromboprophylaxis (OR 0.29, $P = .003$). This result is comparable to GCS, as reported in a Cochrane review (ARR GCS versus no prophylaxis 13%).[5] The meta-analysis comparing NMES to heparin showed that NMES is inferior to UFH (ARR 10.5% with UFH, $P = .02$) in preventing DVT. When used as an adjunct to heparin, NMES confers a 19% ARR of DVT, which is not statistically significant ($P = .08$). However, the results of the meta-analyses should be interpreted in the context of the limitations depicted in the risk of bias table and discussed below.

Limitations of this meta-analysis include the poor trial quality and heterogeneity in methodology, device technology and diagnostic tests. The risk of bias assessment tool rated most of the trials as high risk due to poor randomisation techniques and allocation concealment, which could lead to selection bias. Blinding of outcome assessment was only described in one trial.[25]

The trials included in the meta-analysis involved perioperative patients, except for Merli et al.[26] Whilst NMES was administered only intraoperatively in a majority of trials, other modes of thromboprophylaxis, such as IPC and heparin, could be continued for longer periods of time. This is due to the limitations of NMES technology in the early trials. However, the effect of NMES on venous haemodynamics is comparable between modern and older devices.[15,21,28] Reported limitations of current NMES devices include difficult placement of electrodes,[12] length of electrode-to-lead connector,[12] skin reactions,[12] discomfort due to stimulation of sensory nerves[29] and multiple wire connections increasing the risk of errors.[27]

Paucity of trials and insufficient data precluded subgroup analysis and comparison of incidence of DVT with NMES compared to thromboprophylaxis modalities other than heparin and LMWH. Subgroup analysis on the efficacy of NMES in DVT prophylaxis in different surgical specialities was not possible due to insufficient number of patients.

Diagnostic tests varied reflecting advances in imaging technology. A majority of trials conducted prior to 1990 employed the use of ^{125}I–FUT.[6,20–23,26,28] Although it is very sensitive at detecting distal DVT (84%) and allows repeat measurements, ^{125}I-FUT lacks specificity (54%) and is poor at detecting proximal DVT.[30] Distal DVT is often considered less significant than proximal DVT as patients are often asymptomatic and the below knee clot is less likely to propagate, embolise or lead to PTS.[31] However, its management still remains controversial.[32]

Ascending phlebography is considered the gold standard diagnostic test for DVT, but is expensive, not easily available, technically challenging and associated with contrast reactions. It still had a high technical failure rate (25.6–45.9%)[33–35] when used as the diagnostic test in the recent large multicenter trials on NOACs. Compression ultrasonograpy is widely used in clinical practice and has a sensitivity and specificity of

98 and 95%, respectively, for detecting symptomatic proximal DVT. However, it is operator dependent, requires a cooperative patient and is poor at detecting distal DVT (sensitivity 70%).[36]

Pulmonary perfusion scintigraphy, used as the diagnostic test for PE, has largely been replaced by CTPA as the gold standard for diagnosis of PE, due to high sensitivity and accessibility.[37]

Surgery is a significant risk factor for the development of VTE, with patient and procedure-related risk factors. Age, body mass index and previous history of deep vein thrombosis warrant special caution for VTE prophylaxis. Surgical factors such as duration of surgery, sepsis, malignancy, prolonged ventilation and poor mobility are additional risk factors of VTE.[38] Trials have demonstrated that induction of anaesthesia causes a reduction in venous velocity.[16,28] Laparoscopic surgery, in particular, has detrimental effects on venous haemodynamics as demonstrated by Jorgensen et al.[13]

Several trials have shown that the risk of DVT was highest in the immediate postoperative period and diminishes with increasing mobility.[6,23,28] Therefore, although NMES was only administered intraoperatively in the older trials, this is the period when patients are at greatest risk.

Current pharmacological thromboprophylaxis methods reduce the risk of VTE by approximately 60%.[39] It is estimated to reduce the risk of developing a DVT from 0.30 to 0.08 in high-risk surgical patients.[40] In cardiac surgery, the incidence of DVT on routine screening is 13% despite aggressive pharmacological thromboprophylaxis.[41] In neurosurgery, where the risk of bleeding is equally of concern, the rate of symptomatic VTE remains at 3.5%.[38]

Despite the limitations of the studies included, this paper provides evidence supporting the NICE guidance on the use of NMES in VTE prophylaxis for patients in whom other methods of thromboprophylaxis are contraindicated. It is inferior to heparin as a method of thromboprophylaxis. Evidence is limited for its use as an adjunct to thromboprophylaxis due to the small studies conducted using modern day devices. Large well-designed RCTs would be required to assess the role of NMES in VTE prophylaxis.

Conclusion

This meta-analysis supports the use of NMES devices in reducing the risk of DVT compared to controls receiving no thromboprophylaxis. These include patients with contraindications to pharmacological thromboprophylaxis or at high risk of bleeding. Evidence for the use of NMES as an adjunct to thromboprophylaxis in perioperative patients is lacking.

Acknowledgements

A previous version of this study was presented at the 16th European Venous Forum meeting (2–4 July 2015) and Vascular Society Annual Scientific Meeting (11–13 November 2015). A repeat search has been conducted since and is submitted in this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The department receives funding from Firstkind Ltd and Actegy Healthy Ltd, manufacturers of neuromuscular electrical stimulation devices.

References

1. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; 158: 585–593.
2. Committee HoCH. *The prevention of venous thromboembolism in hospitalised patients*. London: The Stationary Office, 2005.
3. Baldwin MJ, Moore HM, Rudarakanchana N, et al. Post-thrombotic syndrome: a clinical review. *J Thromb Haemost* 2013; 11: 795–805.
4. Virchow R. *Gesammelte Abhandlungen zur wissenschaftlichen Medicin*. Frankfurt-am-Main: Von Meidinger Sohn & Comp., 1856, pp.458–636.
5. Sachdeva A, Dalton M, Amaragiri SV, et al. Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev* 2010; CD001484.
6. Nicolaides AN, Miles C and Hoare M. Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery* 1983; 94: 21–25.
7. Kakkos SK, Warwick D, Nicolaides AN, et al. Combined (mechanical and pharmacological) modalities for the prevention of venous thromboembolism in joint replacement surgery. *J Bone Joint Surg Br* 2012; 94: 729–734.
8. National Institute for Health and Clinical Excellence (NICE). Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital (CG92). National Institute for Health and Clinical Excellence (NICE): London, 2010.
9. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: e195S–226S.

10. Lachmann EA, Rook JL, Tunkel R, et al. Complications associated with intermittent pneumatic compression. *Arch Phys Med Rehabil* 1992; 73: 482–485.
11. Dennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet* 2009; 373: 1958–1965.
12. Broderick BJ, Breathnach O, Condon F, et al. Haemodynamic performance of neuromuscular electrical stimulation (NMES) during recovery from total hip arthroplasty. *J Orthop Surg Res* 2013; 8: 3.
13. Jorgensen JO, Lalak NJ, North L, et al. Venous stasis during laparoscopic cholecystectomy. *Surg Laparosc Endosc* 1994; 4: 128–133.
14. Williams K, Moore H and Davies A. Haemodynamic changes with the use of neuromuscular electrical stimulation compared to intermittent pneumatic compression. *Phlebology* 2014; 30: 365–372.
15. Izumi M, Ikeuchi M, Mitani T, et al. Prevention of venous stasis in the lower limb by transcutaneous electrical nerve stimulation. *Euro J Vasc Endovasc Surg* 2010; 39: 642–645.
16. Doran FS, Drury M and Sivyer A. A simple way to combat the venous stasis which occurs in the lower limbs during surgical operations. *Br J Surg* 1964; 51: 486–492.
17. National Institute for Health and Care Excellence. Medical technologies evaluation programme. NICE medical technologies guidance [MTG19]. *The geko device for reducing the risk of venous thromboembolism*, 2014. Available at: https://www.nice.org.uk/guidance/MTG19/chapter/1-recommendations.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; 62: 1006–1012.
19. Review Manager (RevMan) Version 5.3 ed. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
20. Lindstrom B, Holmdahl C and Jonsson O. Prediction and prophylaxis of postoperative thromboembolism: a comparison between peroperative calf muscle stimulation with groups of impulses and dextran 40. *Br J Surg* 1982; 69: 633–637.
21. Becker J and Schampi B. The incidence of postoperative venous thrombosis of the legs. A comparative study on the prophylactic effect of dextran 70 and electrical calf-muscle stimulation. *Acta Chir Scand* 1973; 139: 357–367.
22. Bostrom S, Holmgren E, Jonsson O, et al. Post-operative thromboembolism in neurosurgery. A study on the prophylactic effect of calf muscle stimulation plus dextran compared to low-dose heparin. *Acta Neurochir* 1986; 80: 83–89.
23. Rosenberg IL, Evans M and Pollock AV. Prophylaxis of postoperative leg vine thrombosis by low dose subcutaneous heparin or peroperative calf muscle stimulation: a controlled clinical trial. *BMJ* 1975; 1: 649–651.
24. Goyal A, Arora S, Batra S, et al. Role of calf muscle stimulation in the prevention of DVT in Indian patients undergoing surgeries for fractures around the hip. *Indian J Orthop* 2012; 46: 542–547.
25. Izumi M, Ikeuchi M, Aso K, et al. Less deep vein thrombosis due to transcutaneous fibular nerve stimulation in total knee arthroplasty: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2015; 23: 3317–3323.
26. Merli GJ, Herbison GJ, Ditunno JF, et al. Deep vein thrombosis: prophylaxis in acute spinal cord injured patients. *Arch Phys Med Rehabil* 1988; 69: 661–664.
27. Velmahos GC, Petrone P, Chan LS, et al. Electrostimulation for the prevention of deep venous thrombosis in patients with major trauma: a prospective randomized study. *Surgery* 2005; 137: 493–498.
28. Nicolaides AN, Kakkar VV, Field ES, et al. Optimal electrical stimulus for prevention of deep vein thrombosis. *BMJ* 1972; 3: 756–758.
29. Clarke Moloney M, Lyons GM, Breen P, et al. Haemodynamic study examining the response of venous blood flow to electrical stimulation of the gastrocnemius muscle in patients with chronic venous disease. *Euro J Vasc Endovasc Surg* 2006; 31: 300–305.
30. Hirsh J, Hull RD and Raskob GE. Clinical features and diagnosis of venous thrombosis. *J Am Coll Cardiol* 1986; 8: 114B–127B.
31. Masuda EM, Kistner RL, Musikasinthorn C, et al. The controversy of managing calf vein thrombosis. *J Vasc Surg* 2012; 55: 550–561.
32. Palareti G. How I treat isolated distal deep vein thrombosis (IDDVT). *Blood* 2014; 123: 1802–1809.
33. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; 5: 2178–2185.
34. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358: 2765–2775.
35. Lassen MR, Raskob GE, Gallus A, et al. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009; 361: 594–604.
36. Kearon C, Julian JA, Newman TE, et al. Noninvasive diagnosis of deep venous thrombosis. McMaster diagnostic imaging practice guidelines initiative. *Ann Intern Med* 1998; 128: 663–677.
37. Le Gal G and Righini M. Controversies in the diagnosis of venous thromboembolism. *J Thromb Haemost* 2015; 13: S259–S265.
38. Kimmell KT and Jahromi BS. Clinical factors associated with venous thromboembolism risk in patients undergoing craniotomy. *J Neurosurg* 2014; 1–8.
39. Agnelli G. Prevention of venous thromboembolism in surgical patients. *Circulation* 2004; 110: IV4–12.
40. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of

VTE events and associated morbidity and mortality. *Thromb Haemost* 2007; 98: 756–764.
41. Schwann TA, Kistler L, Engoren MC, et al. Incidence and predictors of postoperative deep vein thrombosis in cardiac surgery in the era of aggressive thromboprophylaxis. *Ann Thorac Surg* 2010; 90: 760–766; discussion 6–8.

Appendix 1

Ovid search strategy of Embase Classic + Embase 1947 to 2016 week 8 and Ovid MEDLINE ® In-Process and other non-indexed citations and Ovid MEDLINE ®1946 to present.

1	Dvt	21,463
2	Deep vein thrombosis	63,359
3	Deep venous thrombosis	22,435
4	Vte	19,201
5	Venous thrombosis	69,114
6	1 or 2 or 3 or 4 or 5	127,117
7	Electric$	772,106
8	stimulation	1,456,792
9	7 and 8	254,718
10	6 and 9	233
11	Limit 10 to English language	194
12	Limit 11 to human	151
13	Remove duplicates from 12	117