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Neuromuscular electrical stimulation for the prevention of venous thromboembolism (Review)

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[Intervention Review]

Neuromuscular electrical stimulation for the prevention of venous thromboembolism

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ABSTRACT

Background

Venous thromboembolism (VTE) is a serious but preventable cause of morbidity and mortality. Neuromuscular electrical stimulation systems (NMES) for the prevention of VTE may be beneficial for patients in whom pharmacological or standard mechanical prophylaxis methods are contraindicated or are regarded as unsafe or impractical. Although findings of experimental studies suggest that NMES reduce venous stasis, the clinical utility and effectiveness of NMES in VTE prevention remain controversial.

Objectives

To assess the effectiveness of neuromuscular electrical stimulation in the prevention of venous thromboembolism.

Search methods

The Cochrane Vascular Group Information Specialist (CIS) searched the Specialised Register (22 March 2017) and the Cochrane Central Register of Controlled Studies (CENTRAL (2017, Issue 2)). The CIS also searched trial registries for details of ongoing and unpublished studies. The review authors searched the bibliographic lists of relevant articles and reviews to look further for potentially eligible trials.

Selection criteria

We planned to include randomised controlled trials (RCTs) and quasi-randomised trials that compared any form of neuromuscular electrical stimulation as an intervention for VTE prophylaxis (alone or combined with pharmacological or other mechanical methods) versus no prophylaxis and other mechanical or pharmacological methods of VTE prophylaxis.

Data collection and analysis

At least two independent review authors were involved in study selection, data extraction, methodological quality assessment of included studies, and data analysis. We resolved disagreements by discussion between the two review authors. If no agreement could be reached, a third review author acted as an adjudicator. The main outcomes of the review were total deep vein thrombosis (DVT), symptomatic and asymptomatic DVT, pulmonary embolism (PE), total VTE and bleeding (major and minor). The quality of evidence was assessed using the GRADE approach and is indicated in *italics*.

Main results

We included in the review five randomised controlled trials and three quasi-randomised trials, enrolling a total of 904 participants. Among these, four studies included patients undergoing major surgical procedures; one study included patients undergoing surgery for hip fracture under spinal anaesthesia; one study included trauma patients with a contraindication for prophylactic heparin; one study included neurosurgical patients who were operated on under general anaesthesia; and one study included patients with non-functional spinal cord injuries. Overall, eight studies investigated 22 treatment arms. Four studies compared the NMES arm with a no prophylaxis arm, and five studies compared the NMES arm with alternative methods of prophylaxis arms. Alternative methods of prophylaxis included low-dose heparin (5000 IU subcutaneously) - two studies, Dextran 40 - one study, graduated compression stockings (GCS) and intermittent pneumatic compression devices (IPCD) - one study. One study compared combined NMES and low-dose heparin versus no prophylaxis or low-dose heparin alone.

We found no clear difference in risks of total DVT (odds ratio (OR) 1.01, 95% confidence interval (CI) 0.60 to 1.70, P = 0.98; 6 studies, 415 participants; *low-quality evidence*), asymptomatic DVT (OR 1.61, 95% CI 0.40 to 6.43, P = 0.50; 1 study, 89 participants; *low-quality evidence*), symptomatic DVT (OR 0.40, 95% CI 0.02 to 10.07, P = 0.58; 1 study, 89 participants; *low-quality evidence*), PE (OR 1.31, 95% CI 0.38 to 4.48, P = 0.67; 2 studies, 126 participants;*low-quality evidence*), and total VTE (OR 0.92, 95% CI 0.34 to 2.52, P = 0.88; 1 study, 72 participants; *low-quality evidence*) between prophylaxis with NMES and alternative methods of prophylaxis. None of the studies in this comparison reported bleeding.

Compared with no prophylaxis, NMES showed lower risks of total DVT (OR 0.40, 95% CI 0.23 to 0.70, P = 0.02; 4 studies, 576 participants; *moderate-quality evidence*) and total VTE (OR 0.23, 95% CI 0.09 to 0.59, P = 0.002; 1 study, 77 participants; *low-quality evidence*). Data show no clear differences in risk of asymptomatic DVT (OR 0.32, 95% CI 0.06 to 1.62, P = 0.17; 1 study, 200 participants; *low-quality evidence*), symptomatic DVT (OR 0.06, 95% CI 0.00 to 1.36, P = 0.08; 1 study, 160 participants;*low-quality evidence*), or PE (OR 0.36, 95% CI 0.12 to 1.07, P = 0.07; 1 study, 77 participants; *low-quality evidence*) between prophylaxis with NMES and no prophylaxis. None of the studies in this comparison reported bleeding.

In comparison with low-dose heparin, NMES was associated with higher risk of total DVT (OR 2.78, 95% CI 1.19 to 6.48, P = 0.02; 2 studies, 194 participants; *low-quality evidence*), but data were inadequate for other comparisons (NMES vs Dextran 40, NMES vs GCS, or NMES vs IPCD) and for other clinical outcomes such as symptomatic or asymptomatic DVT, PE, total VTE, and bleeding in individual comparisons.

Overall, we judged the quality of available evidence to be low owing to high or unclear risk of bias and imprecise effect estimates due to small numbers of studies and events.

Authors' conclusions

Low-quality evidence shows no clear difference in the risk of DVT between NMES and alternative methods of prophylaxis but suggest that NMES may be associated with lower risk of DVT compared with no prophylaxis (moderate-quality evidence) and higher risk of DVT compared with low-dose heparin (low-quality evidence). The best available evidence about the effectiveness of NMES in the prevention of VTE is not adequately robust to allow definitive conclusions. Adequately powered high-quality randomised controlled trials are required to provide adequately robust evidence.

PLAIN LANGUAGE SUMMARY

Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Background

Formation of unwanted blood clots in the deep veins of the legs is a serious and potentially fatal health problem because blood clots in the legs can travel to the lungs and cause death. Unwanted blood clots in legs can occur as the result of reduced mobility (due to surgery, stroke, injuries, etc.), increased tendency for blood clotting (due to cancer, inherited conditions, etc.), and other factors. Formation of unwanted blood clots in the legs can be prevented by pharmacological methods (heparin, warfarin, etc.) or mechanical methods (specific stockings or devices that help to compress the legs to promote flow of blood within the veins, reducing the risk of blood clotting). Neuromuscular electrical stimulation systems (NMES) deliver electrical impulses via electrodes to the skin over selected muscle groups or nerves to induce an involuntary muscle contraction. NMES are thought to be effective as a mechanical method of preventing blood clots in the legs. Therefore, we aimed to identify available evidence on the effectiveness of NMES compared with other methods in preventing formation of unwanted blood clots.

Study characteristics and key results

We identified eight studies (current until 22 March 2017) enrolling a total of 904 participants that compared NMES with no treatment or with other methods for preventing blood clots, such as low-dose heparin and compression stockings. We found no clear difference in the risk of unwanted blood clots in the legs between NMES and alternative methods of blood clot prevention. We also found that NMES is associated with lower risk of formation of unwanted blood clots in the legs when compared with no treatment, but higher risk of unwanted blood clot formation when compared with heparin. Additional studies are required to obtain stronger evidence.

Quality of the evidence

Overall, the quality of available evidence is low and has been downgraded owing to high or unclear risk of bias, differences between studies, and imprecise effect estimates due to small numbers of studies and events.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

NMES compared to alternative prophylaxis for the prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: NMES
Comparison: alternative prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with alternative prophylaxis	Risk with NMES				
Total DVT Follow-up: mean 11 days	Study population		OR 1.01 (0.60 to 1.70)	415 (6 RCTs)	⊕⊕◯◯ LOW[a,b]	
	170 per 1000	172 per 1000 (110 to 259)				
Asymptomatic DVT Follow-up: 8 days	Study population		OR 1.61 (0.40 to 6.43)	89 (1 RCT)	⊕⊕◯◯ LOW[a,c]	
	82 per 1000	125 per 1000 (34 to 364)				
Symptomatic DVT Follow-up: 8 days	Study population		OR 0.40 (0.02 to 10.07)	89 (1 RCT)	⊕⊕◯◯ LOW[a,c]	
	20 per 1000	8 per 1000 (0 to 173)				
PE Follow-up: mean 4 days	Study population		OR 1.31 (0.38 to 4.48)	126 (2 RCTs)	⊕⊕◯◯ LOW[a,c]	
	70 per 1000	90 per 1000 (28 to 253)				
Total VTE Follow-up: 6 days	Study population		OR 0.92 (0.34 to 2.52)	72 (1 RCT)	⊕⊕◯◯ LOW[a,c]	

	314 per 1000	297 per 1000 (135 to 536)				
Bleeding (major and minor)	see comment	see comment	not estimable	415 (6 RCTs)	-	None of the studies in this comparison reported this outcome

*Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] High or unclear risk of selection bias, performance bias, and detection bias - downgraded by one level.
[b] Moderate level of between-study heterogeneity - downgraded by one level.
[c] Few participants and few events and thus wide confidence intervals - downgraded by one level.

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) is a serious but preventable cause of morbidity and mortality (Arnold 2001), that occurs in approximately 1 per 1000 adults each year (White 2003). Clinical manifestations of VTE - deep vein thrombosis (DVT) and pulmonary embolism (PE) with or without DVT - constitute two-thirds and one-third of cases of VTE, respectively (White 2003). Endothelial injury, hypercoagulable state, and stasis, known as Virchow's triad, form the basis for the pathogenesis of VTE (Virchow 1856). Risk factors contributing to the development of VTE may be hereditary or acquired, and modifiable (e.g. obesity, surgery, trauma, immobility, malignancy) or non-modifiable (e.g. paraplegia, hereditary thrombophilia such as factor V Leiden) (Anderson 2003; Cushman 2007). Hospitalisation is associated with increased risk of VTE due to the presence of multiple risk factors such as immobility, malignancy, infection, and surgery (Anderson 1992). Prophylaxis against VTE is very important for most hospitalised patients, in particular, patients in surgical, trauma, and intensive care units (ICUs), who are at higher risk of VTE as they are more likely to be immobile and to be exposed to the aforementioned VTE risk factors (Guyatt 2012).

Description of the intervention

Mechanical methods of prophylaxis include graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD), and neuromuscular electrical stimulation systems (NMES) (Roderick 2005). GCS and IPCD have been shown to be effective in VTE prophylaxis (Pavon 2016; Sachdeva 2014). However, despite their effectiveness and common use, these methods may be associated with poor patient compliance due to discomfort, excessive heat, itchiness, sweating under the inflatable cuffs, and the potential for peroneal nerve palsy (Faghri 1997; Froimson 2009; Kahn 2002; Laverick 1990; Masri 2004). Neuromuscular electrical stimulation systems deliver electrical energy to skeletal muscle nerve branches, then to muscle units, via superficial electrodes attached to the skin (Baker 1993). Neuromuscular electrical stimulation systems for the prevention of VTE may be beneficial for patients for whom pharmacological or standard mechanical methods of prophylaxis are contraindicated or are regarded as unsafe or impractical.

In terms of limitations, NMES may induce excessive neuromuscular fatigue (Gorgey 2009). Also, muscle contractions induced by NMES are not as unsynchronised and may not be as effective as voluntary muscle contractions. Considering the resistance created by the viscosity of subcutaneous tissue, activation of deeper structures with standard surface stimulation is usually limited (Doucet 2012). Therefore, ideal delivery settings (frequency, energy, etc.) remain unknown. Moreover, although modern devices are thought to be associated with better tolerability, older NMES delivery systems produced painful stimuli, so they could be used only during general anaesthesia (Nicolaides 2013). Owing to lack of comparative data, it is unclear whether NMES would result in better compliance than other methods of mechanical prophylaxis.

How the intervention might work

Experimental studies have shown that NMES increase venous blood velocity and blood flow in stimulated legs, thus reducing venous stasis (Breen 2012; Broderick 2010; Broderick 2013; Griffin 2010; Izumi 2010; Lyons 2002; Moloney 2006; Tucker 2010; Warwick 2013). Although the use of venous velocity as a surrogate outcome for VTE incidence is controversial, this effect may prove beneficial in VTE prevention (Morris 2004). Moreover, neural supply to the veins provides direct antithrombotic effects as the fourth factor not included in Virchow's triad; NMES, via neurogenic pathways, may influence this fourth factor and suppress thrombogenesis (Stefanou 2016). Findings of experimental studies suggest acceptable tolerability of NMES that can potentially lead to good patient compliance (Broderick 2010; Broderick 2013; Moloney 2006; Warwick 2013).

Why it is important to do this review

Although findings of experimental studies suggest that NMES reduce venous stasis, the clinical utility and effectiveness of NMES in VTE prevention remain controversial (Hajibandeh 2015). This review of clinical trials investigating NMES as a mechanical method for VTE prevention will help to address current uncertainties about the benefits of NMES for different patient groups.

A glossary of terms is provided in Appendix 1 to help clarify some of the terms used.

OBJECTIVES

To assess the effectiveness of neuromuscular electrical stimulation in the prevention of venous thromboembolism.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials that investigate any form of neuromuscular electrical stimulation as an intervention for VTE prophylaxis.

Types of participants

Patients undergoing any form of neuromuscular electrical stimulation for the purpose of VTE prevention.

Types of interventions

Intervention of interest

- Any form of neuromuscular electrical stimulation used alone or combined with pharmacological or mechanical methods of VTE prophylaxis, or both.

Comparison

- Mechanical methods of VTE prevention (including GCS or IPCD), pharmacological VTE prophylaxis (including anticoagulant or antithrombotic drugs), both mechanical and pharmacological prophylaxis, or no prophylaxis.

Types of outcome measures

Primary outcomes

- Incidence of DVT (asymptomatic or symptomatic)
- Incidence of PE (with or without DVT)
- Incidence of total VTE (fatal and non-fatal)
- Bleeding (major and minor)

Secondary outcomes

- Device-related adverse effects such as skin irritation or inflammation
- Physiological measurements including changes in tissue oxygen levels, oxygen saturation, heart rate, and blood pressure
- Patient compliance
- Subjective discomfort measured by visual analogue scale (VAS) scores and verbal rating scores (VRS)
- Freedom from VTE at 90 days (symptomatic or asymptomatic)

Diagnosis of PE should be made by ventilation-perfusion scan, computed tomography, pulmonary angiography, or autopsy. DVT should be diagnosed by duplex ultrasonography, venography, or a fibrinogen uptake test.

Major bleeding was defined as fatal bleeding; retroperitoneal, intracranial, or intraocular bleeding; bleeding that causes haemodynamic compromise, a decrease in haemoglobin of 3 g/dL or more, or a decrease in haematocrit of 10% or more; or bleeding that requires intervention or any transfusion of more than 1 unit of packed red blood cells or whole blood. Minor bleeding is defined as gross haematuria, gastrointestinal haemorrhage, haemoptysis, subconjunctival haemorrhage, or epistaxis; haematoma that is larger than 5 cm or leads to prolonged or new hospitalisation; or bleeding that causes a decrease in haemoglobin of 2 to 3 g/dL (Mehran 2011).

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Group Information Specialist (CIS) searched the Specialised Register (22 March 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) via the Cochrane Register of Studies (CRS) (http://www.metaxis.com/CRSWeb/Index.asp). See Appendix 2 for details of the search strategy used to search the CRS. The Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Allied and Complementary Medicine Database (AMED), and through handsearching of relevant journals. The full list of databases, journals, and conference proceedings that have been searched, as well as the search strategies used, is presented in the Specialised Register section of the Cochrane Vascular Module in the Cochrane Library (www.cochranelibrary.com).

In addition, the CIS searched the following trial databases for details of ongoing and unpublished studies.

- World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/).
- ClinicalTrials.gov (http://clinicaltrials.gov/).
- International Standard Registered Clinical/social sTudy Number (ISRCTN) Register (http://www.isrctn.com/).

Searching other resources

We searched the bibliographic lists of relevant articles and reviews for further potentially eligible trials. We contacted manufacturer of the geko™ device (Sky Medical Technology Ltd, Newport, Vermont, USA) for relevant trials.

Data collection and analysis

Selection of studies

Two review authors (Shahab H, Shahin H) independently assessed the title and abstract of articles identified through the literature searches. We retrieved the full texts of relevant reports and selected articles that met the eligibility criteria of our review. We resolved

discrepancies in study selection through discussion between review authors. We consulted a third review author (GA) in the event of disagreement.

Data extraction and management

We created an electronic data extraction spreadsheet consistent with the Cochrane data collection form for intervention reviews. We pilot-tested the spreadsheet in randomly selected articles and adjusted it as needed. Our data extraction spreadsheet included the following.

- Study-related data (first author, year of publication, country of origin of the corresponding author, journal in which the study was published, study design, study size, clinical condition of study participants, type of intervention, duration of VTE prophylaxis, and information about NMES including type of device, frequency, pulse width, charge, and voltage).
- Baseline demographic and clinical information of trial populations.
- Primary and secondary outcome data.

Two review authors (Shahab H, Shahin H) independently collected and recorded data on the data extraction spreadsheet and resolved disagreements by discussion. If no agreement could be reached, we consulted a third review author (JS).

Assessment of risk of bias in included studies

We used the Cochrane tool for assessing risk of bias (Higgins 2011). Two review authors (Shahab H, Shahin H) independently assessed each included study for risk of bias. We assessed all domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias), and for each individual domain, we classified studies as having low, unclear, or high risk of bias. We resolved disagreements by discussion between the two review authors (Shahab H, Shahin H). If no agreement could be reached, a third review author (FT) acted as an adjudicator.

Measures of treatment effect

The primary outcomes in our review (frequency of DVT, PE, VTE, bleeding, and device-related adverse effects) were dichotomous variables; therefore, we calculated the odds ratio (OR), which represents the odds of an adverse event in the NMES group compared with the non-NMES group, as the summary measure. An OR of less than one would favour the NMES. For continuous parameters such as compliance and discomfort measurements, we planned to calculate the mean difference (MD) between NMES and non-NMES groups, unless trials reported different scales of measurement, in which case we planned to compute the standardised mean difference (SMD).

Unit of analysis issues

We used the individual patient as the unit of analysis in our review. If any included study in our review reported outcomes related to a mixture of units of analysis, we extracted only data relevant to our unit of analysis. We excluded studies that randomised individual legs instead of individual participants, as we believe that two legs of one participant are not independent.

Dealing with missing data

We recorded information about dropouts and withdrawals and other missing data; if not reported, we contacted study authors to ask for this information. The final analysis was based on intention-to-treat data from individual clinical trials.

Assessment of heterogeneity

We assessed heterogeneity among studies by using the Chi² test. We quantified inconsistency by calculating I^2 and interpreted it using the following guide (Higgins 2011).

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We planned to use the Egger's regression intercept to assess reporting bias in our review. We planned to construct funnel plots and evaluate their symmetry to visually assess publication bias, as long as a sufficient number of trials (more than 10) were available.

Data synthesis

We used Review Manager 5.3 software for data synthesis (RevMan 2014). The first review author (Shahab H) entered extracted data into Review Manager, and the second review author (Shahin H) independently checked the data. We used random-effects or fixed-effect modelling, as appropriate, for analysis. We applied random-effects models if we identified considerable heterogeneity among studies, as defined by Higgins 2011. We reported results in a forest plot with 95% confidence intervals (CIs).

Subgroup analysis and investigation of heterogeneity

If possible, we planned to perform separate analyses for the following subgroups.

- Surgical patients.
- Trauma patients.
- ICU patients.
- Patients with chronic venous disease.
- Patients with neurological disorders.

If possible, we planned to perform separate analyses for individual NMES devices, old NMES devices (those no longer available for use at present), and contemporary NMES devices.

Sensitivity analysis

To explore potential sources of heterogeneity and to assess the robustness of our results, we performed additional analyses for outcomes reported by at least four studies. These included repeating the primary analysis using random-effects and fixed-effect models, calculating the pooled risk ratio (RR) or risk difference (RD) for each dichotomous variable, and assessing the effect of each study on overall effect size and heterogeneity by repeating the analysis after removing one study at a time. We also performed sensitivity analyses that excluded studies at high risk of bias.

'Summary of findings' table

We constructed a table to compile and summarise the best evidence on relevant outcomes of comparisons of NMES versus other methods of thromboprophylaxis. We considered study populations consisting of patients with surgical, trauma, or medical conditions. We selected the most important and clinically relevant outcomes (both desirable and undesirable) thought to be essential for decision-making for inclusion in the 'Summary of findings' table. We have described these in the Types of outcome measures section. We calculated assumed control intervention risks by using the mean number of events in control groups of selected studies for each outcome. We used the system developed by the Grading of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) in grading the quality of evidence as high, moderate, low, and very low, based on within-study risk of bias, directness of evidence, heterogeneity, precision of effects estimates, and risk of publication bias (Atkins 2004; GRADEproGDT).

RESULTS

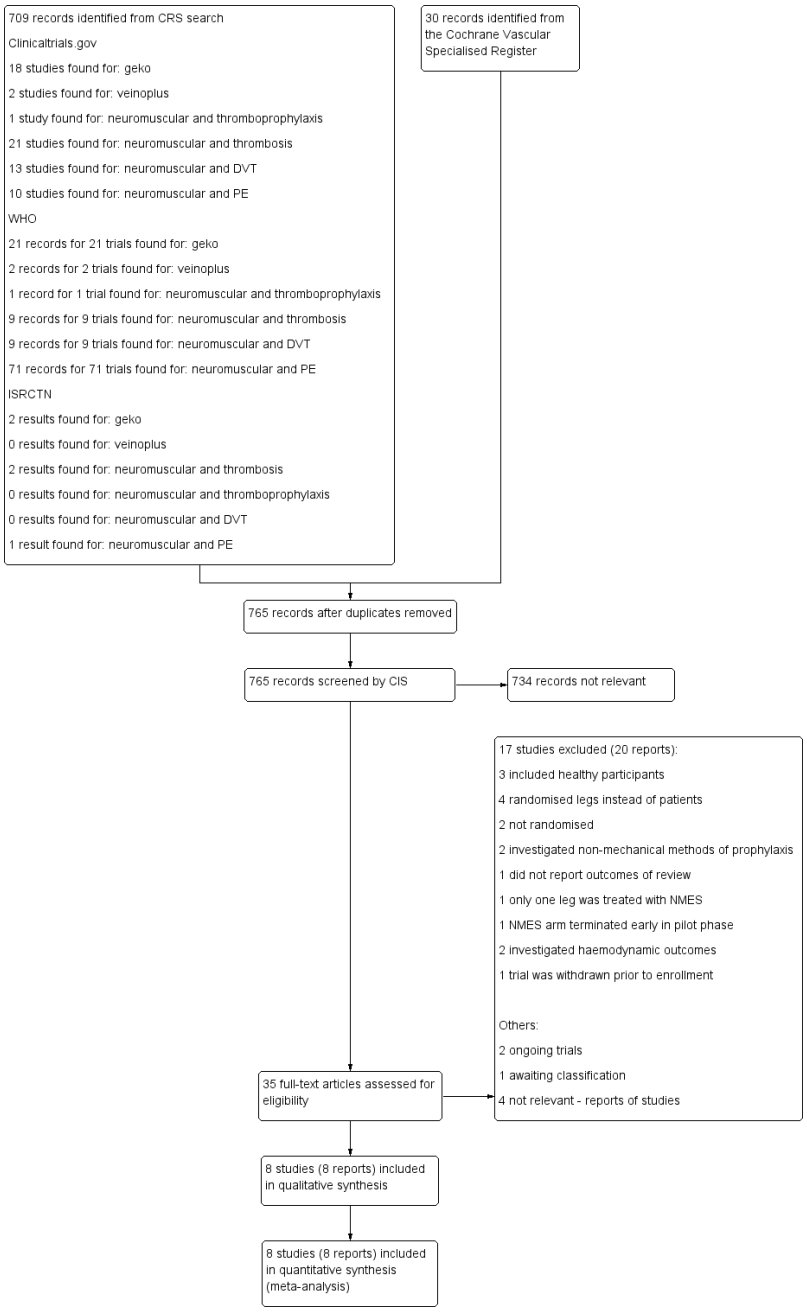
Description of studies

We have provided characteristics of the included studies in the Characteristics of included studies section.

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

We included five RCTs - Hou 2013; Kiudelis 2002; Lindstrom 1982; Merli 1988; Velmahos 2005 - and three quasi-randomised trials - Bostrom 1986; Goyal 2012; Rosenberg 1975 - enrolling a total of 904 participants. Among these, four studies included patients undergoing major surgical procedures (Hou 2013; Kiudelis 2002, Lindstrom 1982; Rosenberg 1975); one included patients undergoing surgery for hip fracture under spinal anaesthesia (Goyal 2012); one included trauma patients with a contraindication for prophylactic heparin (Velmahos 2005); one included neurosurgical patients who were operated on under general anaesthesia (Bostrom 1986); and one included patients with non-functional spinal cord injuries (Merli 1988). We have reported in Table 1 the NMES delivery settings used in the included studies.

Four studies compared NMES versus no prophylaxis (Goyal 2012; Hou 2013; Lindstrom 1982; Rosenberg 1975). Two studies compared NMES versus low-dose heparin (5000 IU subcutaneously) (Bostrom 1986; Rosenberg 1975). One study compared NMES versus Dextran 40 (Lindstrom 1982). One study compared NMES with no prophylaxis or with low-dose heparin (Velmahos 2005). One study compared combined NMES and low-dose heparin versus no prophylaxis or low-dose heparin alone (Merli 1988). One study compared NMES versus GCS and IPCD (Kiudelis 2002). Six studies delivered NMES perioperatively (Bostrom 1986; Goyal 2012; Hou 2013; Kiudelis 2002; Lindstrom 1982; Rosenberg 1975).

In terms of methods to diagnose DVT, two studies used duplex ultrasonography (Goyal 2012; Hou 2013); one used either duplex ultrasonography or venography (Velmahos 2005); four used the fibrinogen uptake test with or without venography (Bostrom 1986; Lindstrom 1982; Merli 1988; Rosenberg 1975); and one used venous occlusion plethysmography (Kiudelis 2002). The median duration of follow-up in the included studies was seven days (Interquartile range: five).

Excluded studies

We excluded 17 studies from the review (Browse 1970; Czyrny 2010; Doran 1967; Doran 1970; Faghri 1998; Hou 2014; Izumi 2014; Jansen 1972; Kaplan 2002; Lobastov 2014; Morita 2006; NCT02425917; Nicolaides 1983; Ojima 2017; Pambianco 1995; Rosengarten 1975; Yilmaz 2016). Among these, we excluded three studies because they included healthy participants (Czyrny 2010; Kaplan 2002; Morita 2006); four studies because they randomised legs instead of participants (Browse 1970; Doran 1967; Doran 1970; Nicolaides 1983); two studies because they were non-randomised studies (Faghri 1998; Lobastov 2014); two studies because they investigated non-mechanical methods of prophylaxis only (Jansen 1972; Rosengarten 1975); one study because only one leg was treated with NMES (Izumi 2014); one study because the NMES arm was terminated early in the pilot phase (Pambianco 1995); one study because researchers did not report the outcomes specified in this review (Hou 2014); two studies because they investigated haemodynamic outcomes and were powered for these outcomes only (Ojima 2017; Yilmaz 2016); and one study because the trial had been withdrawn before enrolment (NCT02425917). Moreover, we assessed three articles containing data about unpublished trials for potentially eligible trials, but we identified no eligible trials, as all trials included healthy participants (Firstkind 2013; NICE 2011; Summers 2015).

In addition, we identified two relevant ongoing trials, results of which were not available at the time of this writing (ISRCTN95441725; NCT01935414). One study is still awaiting classification because the study has been completed but study results are not yet available (NCT01835990).

Risk of bias in included studies

We have presented the summary and results of methodological quality assessment graphically in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

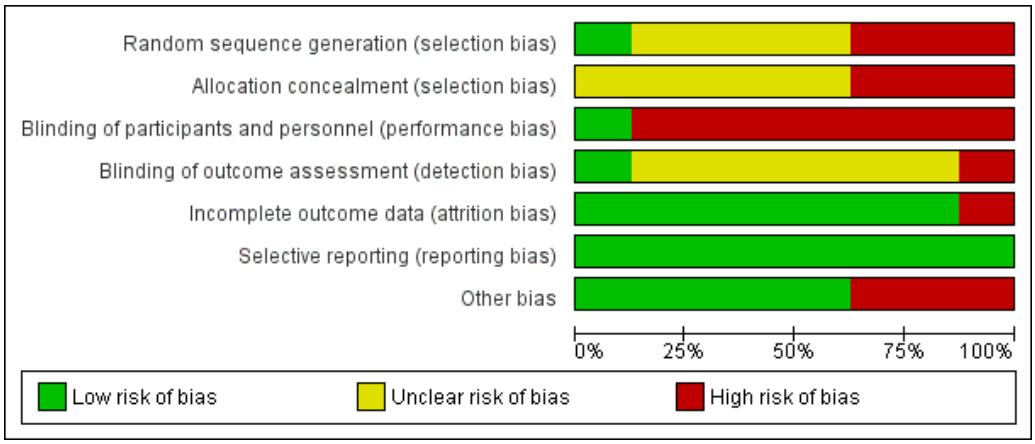
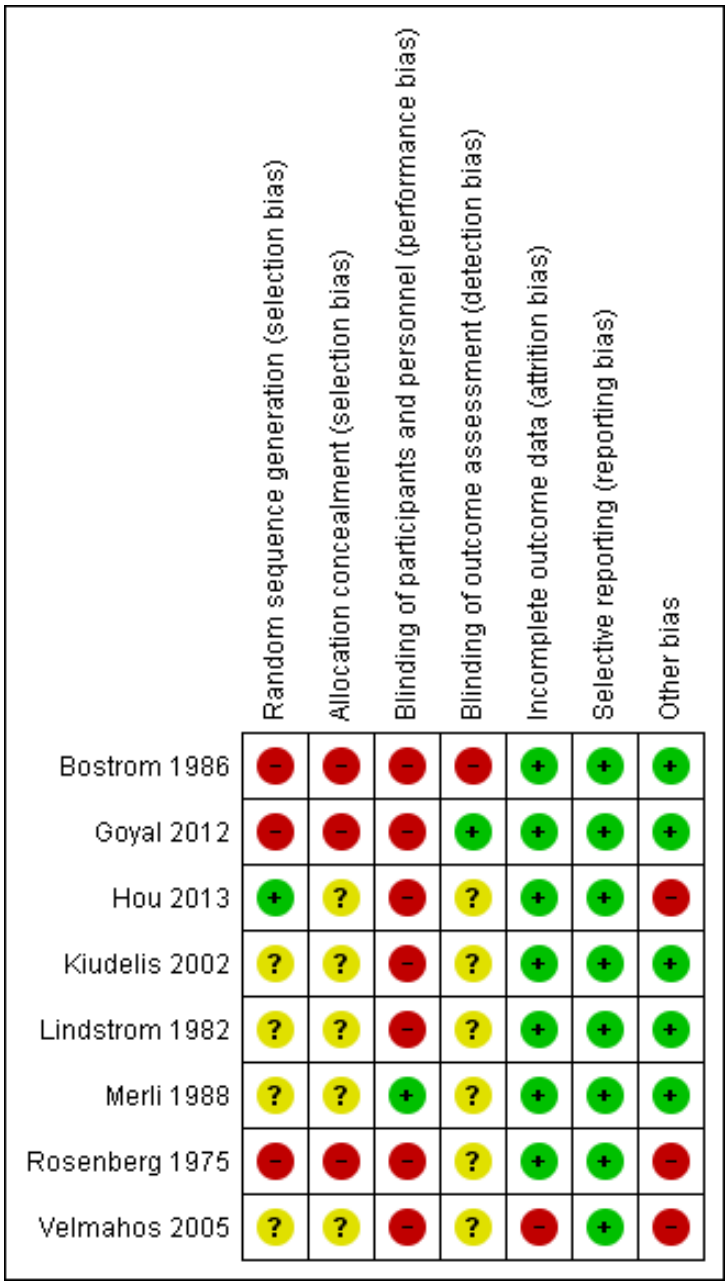


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In terms of random sequence generation, we judged one study to be at low risk of selection bias (Hou 2013); three studies to be at high risk of selection bias because of inappropriate method of randomisation (Bostrom 1986; Goyal 2012; Rosenberg 1975); and four studies to be at unclear risk of selection bias because they did not report information about methods of randomisation (Kiudelis 2002; Lindstrom 1982; Merli 1988; Velmahos 2005).

In terms of allocation concealment, we judged three studies to be at high risk of bias (Bostrom 1986; Goyal 2012; Rosenberg 1975). The remaining studies did not provide adequate information about allocation concealment; therefore, risk of bias is unclear in these studies (Hou 2013; Kiudelis 2002; Lindstrom 1982; Merli 1988; Velmahos 2005).

Blinding

We judged risk of performance bias to be low in one study (Merli 1988). We judged risk of performance bias to be high in seven studies because trialists performed no blinding of participants and personnel (Bostrom 1986; Goyal 2012; Hou 2013; Kiudelis 2002; Lindstrom 1982; Rosenberg 1975; Velmahos 2005).

We judged risk of detection bias to be low in Goyal 2012 and high in Bostrom 1986. We were not able to assess risk of detection bias in the other studies, as reporting about blinding of outcome assessment was insufficient (Hou 2013; Kiudelis 2002; Lindstrom 1982; Merli 1988; Rosenberg 1975; Velmahos 2005).

Incomplete outcome data

We judged seven studies to be at low risk of attrition bias (Bostrom 1986; Goyal 2012; Hou 2013; Kiudelis 2002; Lindstrom 1982; Merli 1988; Rosenberg 1975). We judged risk of attrition bias to be high in one study because missing data were not balanced in numbers across intervention groups (Velmahos 2005).

Selective reporting

We judged risk of reporting bias in all included studies as low because although the protocols of the included studies were not available, it is clear that published reports included all expected outcomes.

Other potential sources of bias

We judged three studies to be potentially at high risk of bias because they were Industry sponsored (Hou 2013; Rosenberg 1975; Velmahos 2005). We deemed the remaining five studies to be at low risk of bias, as we identified no other potential sources of bias (Bostrom 1986; Goyal 2012; Kiudelis 2002; Lindstrom 1982; Merli 1988).

Effects of interventions

See: **Summary of findings for the main comparison** NMES compared to alternative prophylaxis for the prevention of venous thromboembolism; **Summary of findings 2** NMES compared to no prophylaxis for prevention of venous thromboembolism; **Summary of findings 3** NMES compared to low-dose heparin for the prevention of venous thromboembolism; **Summary of findings 4** NMES compared to Dextran 40 for the prevention of venous thromboembolism; **Summary of findings 5** Combined NMES and low-dose heparin compared to no prophylaxis for the prevention of venous thromboembolism; **Summary of findings 6** Combined NMES and low-dose heparin compared to low-dose heparin for the prevention of venous thromboembolism; **Summary of findings 7** NMES compared to GCS for the prevention of venous thromboembolism; **Summary of findings 8** NMES compared to IPCD for the prevention of venous thromboembolism

Available data allowed us to perform eight comparisons. We have presented details about these comparisons in the Data and analyses section. In brief, we present data comparing NMES versus no prophylaxis, NMES versus alternative prophylaxis that is combining all studies using an alternative prophylaxis as a comparator, and NMES versus individual comparisons making up the alternative prophylaxis.

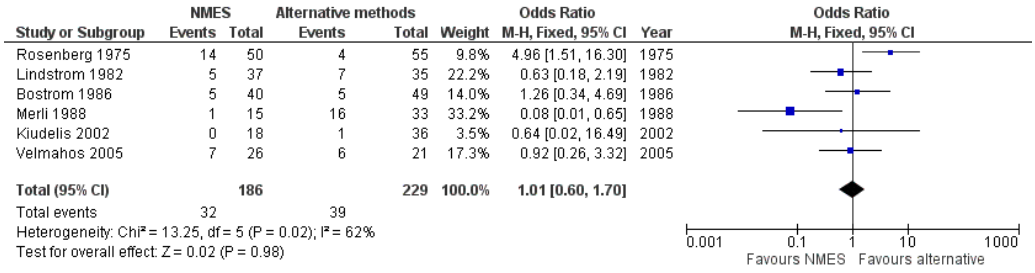
NMES versus alternative prophylaxis

This comparison includes all studies comparing NMES (alone or in combination with other methods of prophylaxis) versus any other method of VTE prophylaxis (Bostrom 1986; Kiudelis 2002; Lindstrom 1982; Merli 1988; Rosenberg 1975; Velmahos 2005).

Total DVT

Six studies, enrolling a total of 415 participants, reported total DVT (Bostrom 1986; Kiudelis 2002; Lindstrom 1982; Merli 1988; Rosenberg 1975; Velmahos 2005). Data show no differences in risk of total DVT between NMES and alternative prophylaxis groups (odds ratio (OR) 1.01, 95% confidence interval (CI) 0.60 to 1.70, P = 0.98; low-quality evidence). Studies show a moderate level of heterogeneity (I^2 = 62%, P = 0.02) (Analysis 1.1) (Figure 4).

Figure 4. Forest plot of comparison: 1 NMES versus alternative prophylaxis, outcome: 1.1 Total DVT.



Asymptomatic DVT

One study, enrolling a total of 89 participants, reported asymptomatic DVT (Bostrom 1986). Data show no clear differences in the risk of asymptomatic DVT between NMES and alternative prophylaxis groups (OR 1.61, 95% CI 0.40 to 6.43, P = 0.50; low-quality evidence) (Analysis 1.2).

Symptomatic DVT

One study, enrolling a total of 89 participants, reported symptomatic DVT (Bostrom 1986). Data show no clear differences in the risk of symptomatic DVT between NMES and alternative prophylaxis groups (OR 0.40, 95% CI 0.02 to 10.07, P = 0.58; low-quality evidence) (Analysis 1.3).

PE

Two studies, enrolling a total of 126 participants, reported PE (Kiudelis 2002; Lindstrom 1982). Data show no clear differences in the risk of PE between NMES and alternative prophylaxis groups (OR 1.31, 95% CI 0.38 to 4.48, P = 0.67; low-quality evidence). Studies show a low level of heterogeneity (I^2 = 0%, P = 0.64) (Analysis 1.4).

Total VTE

One study, enrolling a total of 72 participants, reported total VTE (Lindstrom 1982). Data show no clear differences in the risk of total VTE between NMES and alternative prophylaxis groups (OR 0.92, 95% CI 0.34 to 2.52, P = 0.88; low-quality evidence) (Analysis 1.5).

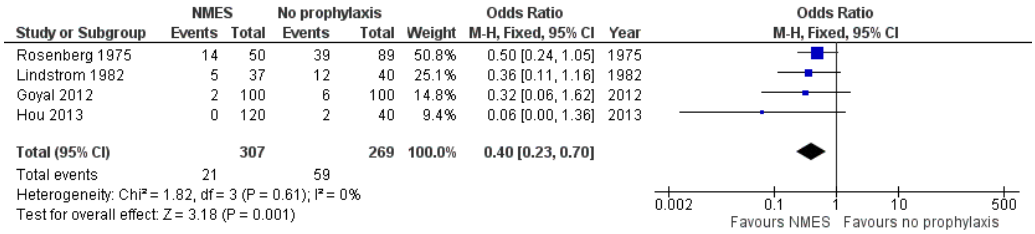
The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

NMES versus no prophylaxis

Total DVT

Four studies, enrolling a total of 576 participants, reported total DVT (Goyal 2012; Hou 2013; Lindstrom 1982; Rosenberg 1975). Prophylaxis with NMES was associated with lower risk of DVT than no prophylaxis (OR 0.40, 95% CI 0.23 to 0.70, P = 0.001; moderate-quality evidence). Studies show a low level of heterogeneity (I^2 = 0%, P = 0.61) (Analysis 2.1) (Figure 5).

Figure 5. Forest plot of comparison: 2 NMES versus no prophylaxis, outcome: 2.1 Total DVT.



Asymptomatic DVT

One study, enrolling a total of 200 participants, reported asymptomatic DVT (Goyal 2012). Data show no clear differences in the risk of asymptomatic DVT between NMES and no prophylaxis groups (OR 0.32, 95% CI 0.06 to 1.62, P = 0.17; low-quality evidence) (Analysis 2.2).

Symptomatic DVT

One study, enrolling a total of 160 participants, reported symptomatic DVT (Hou 2013). Data show no clear differences in the risk of symptomatic DVT between NMES and no prophylaxis groups (OR 0.06, 95% CI 0.00 to 1.36, P = 0.08; low-quality evidence) (Analysis 2.3).

PE

One study, enrolling a total of 77 participants, reported PE (Lindstrom 1982). Data show no clear differences in the risk of PE between NMES and no prophylaxis groups (OR 0.36, 95% CI 0.12 to 1.07, P = 0.07; low-quality evidence) (Analysis 2.4).

Total VTE

One study, enrolling a total of 77 participants, reported total VTE (Lindstrom 1982). Risk of total VTE was lower in the NMES group than in the no prophylaxis group (OR 0.23, 95% CI 0.09 to 0.59, P = 0.002; low-quality evidence) (Analysis 2.5).
The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

NMES versus low-dose heparin

Total DVT

Two studies, enrolling a total of 194 participants, reported total DVT (Bostrom 1986; Rosenberg 1975). Prophylaxis with NMES was associated with higher risk of DVT than prophylaxis with low-dose heparin (OR 2.78, 95% CI 1.19 to 6.48, P = 0.02; low-quality evidence). Studies show a moderate level of heterogeneity (I^2 = 57%, P = 0.13) (Analysis 3.1).

Asymptomatic DVT

One study, enrolling a total of 89 participants, reported asymptomatic DVT (Bostrom 1986). Data show no clear differences in the risk of asymptomatic DVT between NMES and low-dose heparin groups (OR 1.61, 95% CI 0.40 to 6.43, P = 0.50; low-quality evidence) (Analysis 3.2).

Symptomatic DVT

One study, enrolling a total of 89 participants, reported symptomatic DVT (Bostrom 1986). Data show no clear differences in the risk of symptomatic DVT between NMES and low-dose heparin groups (OR 0.40, 95% CI 0.02 to 10.07, P = 0.58; low-quality evidence) (Analysis 3.3).
The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

NMES versus Dextran 40

Total DVT

One study, enrolling a total of 72 participants, reported total DVT (Lindstrom 1982). Data show no clear differences in the risk of DVT between NMES and Dextran 40 groups (OR 0.63, 95% CI 0.18 to 2.19, P = 0.46; low-quality evidence) (Analysis 4.1).

PE

One study, enrolling a total of 72 participants, reported PE (Lindstrom 1982). Data show no clear differences in the risk of PE between NMES and Dextran 40 groups (OR 1.50, 95% CI 0.39 to 5.84, P = 0.56; low-quality evidence) (Analysis 4.2).

Total VTE

One study, enrolling a total of 72 participants, reported total VTE (Lindstrom 1982). Data show no clear differences in the risk of total VTE between NMES and Dextran 40 groups (OR 0.92, 95% CI 0.34 to 2.52, P = 0.88; low-quality evidence) (Analysis 4.3).
The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

Combined NMES and low-dose heparin versus no prophylaxis

Total DVT

One study, enrolling a total of 32 participants, reported total DVT (Merli 1988). NMES combined with low-dose heparin was associated with lower risk of DVT when compared with no prophylaxis (OR 0.08, 95% CI 0.01 to 0.76, P = 0.03; low-quality evidence) (Analysis 5.1).
The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

Combined NMES and low-dose heparin versus low-dose heparin

Total DVT

One study, enrolling a total of 31 participants, reported total DVT (Merli 1988). NMES combined with low-dose heparin was associated with lower risk of DVT when compared with low-dose heparin alone (OR 0.07, 95% CI 0.01 to 0.68, P = 0.02; low-quality evidence) (Analysis 6.1).

The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

NMES versus GCS

Total DVT

One study, enrolling a total of 36 participants, reported total DVT (Kiudelis 2002). Data show no clear differences in the risk of DVT between NMES and GCS groups (OR 0.32, 95% CI 0.01 to 8.27, P = 0.49; low-quality evidence) (Analysis 7.1).

PE

One study, enrolling a total of 36 participants, reported PE (Kiudelis 2002). Data show no clear differences in the risk of PE between NMES and GCS groups (OR 0.32, 95% CI 0.01 to 8.27, P = 0.49; low-quality evidence) (Analysis 7.2).

The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

NMES versus IPCD

Total DVT

One study, enrolling a total of 36 participants, reported total DVT (Kiudelis 2002). Owing to the occurrence of no DVT in either group, the OR was not estimable (Analysis 8.1).

PE

One study, enrolling a total of 36 participants, reported PE (Kiudelis 2002). Owing to the occurrence of no PE in either group, the OR was not estimable (Analysis 8.2).

The included studies did not report the other primary and secondary outcome measures of this review for this comparison.

Subgroup analysis

We planned to perform subgroup analyses for surgical patients, trauma patients, ICU patients, patients with chronic venous disease, and patients with neurological disorders. However, after considering the limited number of studies, the quality of available data, the heterogeneity of included populations, NMES delivery systems, and the duration and frequency of stimulation, we decided not to perform any subgroup analyses in this review.

Available data did not allow for separate analyses based on individual NMES devices, old NMES devices (those no longer available for use at present), and contemporary NMES devices.

Sensitivity analysis

After considering the limited number of included studies, we performed sensitivity analysis for only one outcome measure in two comparisons (i.e. comparisons for which more than four studies reported the outcome) (Analysis 1.1; Analysis 2.1).

Total DVT in NMES versus alternative prophylaxis comparison

Use of random-effects or fixed-effect models did not affect the direction of the effect size (Analysis 1.1). Moreover, the direction of the effect size remained unchanged when pooled RRs or RDs were calculated. Removing one study at a time did not change the direction of the effect size and overall heterogeneity in this analysis. Excluding studies judged to be at high risk of bias did not change the direction of the effect size.

Total DVT in NMES versus no prophylaxis comparison

Use of random-effects or fixed-effect models did not affect the direction of the effect size (Analysis 2.1). Moreover, the direction of the effect size remained unchanged when pooled RRs or RDs were calculated. Removing one study at a time did not change the direction of the effect size and overall heterogeneity in this analysis. Excluding studies judged to be at high risk of bias did not change the direction of the effect size.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

NMES compared to no prophylaxis for prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: NMES
Comparison: no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no prophylaxis	Risk with NMES				
Total DVT Follow-up: mean 7 days	Study population		OR 0.40 (0.23 to 0.70)	576 (4 RCTs)	⊕⊕⊕◯ MODERATE[a]	
	219 per 1000	101 per 1000 (61 to 164)				
Asymptomatic DVT Follow-up: 7 days	Study population		OR 0.32 (0.06 to 1.62)	200 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	60 per 1000	20 per 1000 (4 to 94)				
Symptomatic DVT Follow-up: 7 days	Study population		OR 0.06 (0.00 to 1.36)	160 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	50 per 1000	3 per 1000 (0 to 67)				
PE Follow-up: 6 days	Study population		OR 0.36 (0.12 to 1.07)	77 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	350 per 1000	162 per 1000 (61 to 366)				
Total VTE Follow-up: 6 days	Study population		OR 0.23 (0.09 to 0.59)	77 (1 RCT)	⊕⊕◯◯ LOW[a,b]	

	650 per 1000	299 per 1000 (143 to 523)				
Bleeding (major and minor)	see comment	see comment	not estimable	576 (4 RCTs)	-	None of the studies in this comparison reported this outcome

*Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] High or unclear risk of selection bias, performance bias, and detection bias - downgraded by one level.
[b] Few participants and few events and thus wide confidence intervals - downgraded by one level.

NMES compared to low-dose heparin for the prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: NMES
Comparison: low-dose heparin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with low-dose heparin	Risk with NMES				
Total DVT Follow-up: mean 7 days	Study population		OR 2.78 (1.19 to 6.48)	194 (2 RCTs)	⊕⊕◯◯ LOW[a,b]	
	87 per 1000	208 per 1000 (101 to 380)				
Asymptomatic DVT Follow-up: 8 days	Study population		OR 1.61 (0.40 to 6.43)	89 (1 RCT)	⊕⊕◯◯ LOW[b,c]	
	82 per 1000	125 per 1000 (34 to 364)				
Symptomatic DVT Follow-up: 8 days	Study population		OR 0.40 (0.02 to 10.07)	89 (1 RCT)	⊕⊕◯◯ LOW[b,c]	
	20 per 1000	8 per 1000 (0 to 173)				
PE	see comment	see comment	not estimable	194 (2 RCTs)	-	None of the studies in this comparison reported this outcome
Total VTE	see comment	see comment	not estimable	194 (2 RCTs)	-	None of the studies in this comparison reported this outcome

Bleeding (major and minor)	see comment	see comment	not estimable	194 (2 RCTs)	-	None of the studies in this comparison reported this outcome

*Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] High or unclear risk of selection bias, performance bias, and detection bias - downgraded by one level.
[b] Few participants and few events and thus wide confidence intervals - downgraded by one level.
[c] High or unclear risk of selection bias and detection bias - downgraded by one level.

NMES compared to Dextran 40 for the prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: NMES
Comparison: Dextran 40

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Dextran 40	Risk with NMES				
Total DVT Follow-up: 6 days	Study population		OR 0.63 (0.18 to 2.19)	72 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	200 per 1000	136 per 1000 (43 to 354)				
Asymptomatic DVT	see comment	see comment	not estimable	72 (1 RCT)	-	The single study in this comparison did not report this outcome
Symptomatic DVT	see comment	see comment	not estimable	72 (1 RCT)	-	The single study in this comparison did not report this outcome
PE Follow-up: 6 days	Study population		OR 1.50 (0.39 to 5.84)	72 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	114 per 1000	162 per 1000 (48 to 430)				
Total VTE Follow-up: 6 days	Study population		OR 0.92 (0.34 to 2.52)	72 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	314 per 1000	297 per 1000 (135 to 536)				

Bleeding (major and minor)	see comment	see comment	not estimable	72 (1 RCT)	-	The single study in this comparison did not report this outcome

Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. *The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect,

[a] High or unclear risk of selection bias, performance bias, and detection bias - downgraded by one level.
[b] Single study, few participants, and few events and thus wide confidence intervals - downgraded by one level.

Combined NMES and low-dose heparin compared to no prophylaxis for the prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: combined NMES and low-dose heparin
Comparison: no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no prophylaxis	Risk with combined NMES and low-dose heparin				
Total DVT Follow-up: 28 days	Study population		OR 0.08 (0.01 to 0.76)	32 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	471 per 1000	66 per 1000 (9 to 403)				
Asymptomatic DVT	see comment	see comment	not estimable	32 (1 RCT)	-	The single study in this comparison did not report this outcome
Symptomatic DVT	see comment	see comment	not estimable	32 (1 RCT)	-	The single study in this comparison did not report this outcome
PE	see comment	see comment	not estimable	32 (1 RCT)	-	The single study in this comparison did not report this outcome
Total VTE	see comment	see comment	not estimable	32 (1 RCT)	-	The single study in this comparison did not report this outcome

Bleeding (major and minor)	see comment	see comment	not estimable	32 (1 RCT)	-	The single study in this comparison did not report this outcome

*Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] High or unclear risk of selection bias and detection bias - downgraded by one level.
[b] Single study, few participants, and few events and thus wide confidence intervals - downgraded by one level.

Combined NMES and low-dose heparin compared to low-dose heparin for the prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: combined NMES and low-dose heparin
Comparison: low-dose heparin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with low-dose heparin	Risk with combined NMES and low-dose heparin				
Total DVT Follow-up: 28 days	Study population		OR 0.07 (0.01 to 0.68)	31 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
	500 per 1000	65 per 1000 (10 to 405)				
Asymptomatic DVT	see comment	see comment	not estimable	31 (1 RCT)	-	The single study in this comparison did not report this outcome
Symptomatic DVT	see comment	see comment	not estimable	31 (1 RCT)	-	The single study in this comparison did not report this outcome
PE	see comment	see comment	not estimable	31 (1 RCT)	-	The single study in this comparison did not report this outcome
Total VTE	see comment	see comment	not estimable	31 (1 RCT)	-	The single study in this comparison did not report this outcome

Bleeding (major and minor)	see comment	see comment	not estimable	31 (1 RCT)	-	The single study in this comparison did not report this outcome

*Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] High or unclear risk of selection bias and detection bias - downgraded by one level.
[b] Single study, few participants, and few events and thus wide confidence intervals - downgraded by one level.

NMES compared to GCS for the prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: NMES
Comparison: GCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with GCS	Risk with NMES				
Total DVT Follow-up: 1 day	Study population 56 per 1000	18 per 1000 (1 to 327)	OR 0.32 (0.01 to 8.27)	36 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
Asymptomatic DVT	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome
Symptomatic DVT	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome
PE Follow-up: 1 day	Study population 56 per 1000	18 per 1000 (1 to 327)	OR 0.32 (0.01 to 8.27)	36 (1 RCT)	⊕⊕◯◯ LOW[a,b]	
Total VTE	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome
Bleeding (major and minor)	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome

*Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; GCS: graduated compression stockings; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] High or unclear risk of selection bias, performance bias, and detection bias - downgraded by one level.
[b] Single study, few participants, and few events and thus wide confidence intervals - downgraded by one level.

NMES compared to IPCD for the prevention of venous thromboembolism

Patient or population: participants at risk of venous thromboembolism
Setting: hospital, secondary care
Intervention: NMES
Comparison: IPCD

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with IPCD	Risk with NMES				
Total DVT Follow-up: 1 day	Study population		not estimable	36 (1 RCT)	⊕⊕◯◯ LOW[a,b]	No DVT events were recorded.
	see comment	see comment				
Asymptomatic DVT	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome
Symptomatic DVT	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome
PE Follow-up: 1 day	Study population		not estimable	36 (1 RCT)	⊕⊕◯◯ LOW[a,b]	No PE events were recorded.
	see comment	see comment				
Total VTE	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome
Bleeding (major and minor)	see comment	see comment	not estimable	36 (1 RCT)	-	None of the studies in this comparison reported this outcome

*Assumed control intervention risks were calculated by the mean number of events in control groups of selected studies for each outcome. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DVT: deep vein thrombosis; IPCD: intermittent pneumatic compression devices; NMES: neuromuscular electrical stimulation; OR: odds ratio; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] High or unclear risk of selection bias, performance bias, and detection bias - downgraded by one level.
[b] Single study, few participants, and few events - downgraded by one level.

DISCUSSION

Summary of main results

We conducted a systematic review of randomised controlled trials and quasi-randomised trials of reported outcomes to evaluate the effectiveness of neuromuscular electrical stimulation systems (NMES) in the prevention of venous thromboembolism (VTE). We included eight trials, enrolling a total of 904 participants. Our results show no differences in the risk of deep vein thrombosis (DVT) between NMES and alternative methods of prophylaxis (odds ratio (OR) 1.01, 95% confidence interval (CI) 0.60 to 1.70, P = 0.98; low-quality evidence; 6 studies, 415 participants). Our analysis also shows that prophylaxis with NMES was associated with lower risk of DVT compared with no prophylaxis (OR 0.40, 95% CI 0.23 to 0.70, P = 0.02; moderate-quality evidence; 4 studies, 576 participants); however, prophylaxis with NMES was found to be associated with higher risk of DVT than prophylaxis with low-dose heparin (OR 2.78, 95% CI 1.19 to 6.48, P = 0.02; low-quality evidence; 2 studies, 194 participants). Available evidence did not allow us to reach a conclusion regarding the effectiveness of NMES in comparison with other mechanical or pharmacological methods of prophylaxis owing to limited data. The effect of NMES on some clinical outcomes such as symptomatic or asymptomatic DVT, pulmonary embolism (PE), total VTE, bleeding, or patient compliance remains unknown. The included studies were considerably heterogeneous in terms of participant populations and settings; devices and settings used to deliver NMES; duration and frequency of electrical stimulation; and methods used to diagnose VTE.

Overall completeness and applicability of evidence

The best available evidence about the effectiveness of NMES in the prevention of VTE is not adequately robust to allow definitive conclusions. Available evidence shows that NMES when compared with no prophylaxis was associated with lower risk of DVT; this suggests that NMES may be beneficial for individuals who are at high risk for VTE and are unable to receive any other mechanical or pharmacological methods of prophylaxis. However, the available evidence is derived from a very small number of studies with generally small sample sizes. We found inadequate evidence on the effectiveness of NMES versus commonly used mechanical methods of prophylaxis such as graduated compression stockings (GCS) and intermittent pneumatic compression devices (IPCD), which have been shown to be effective in VTE prophylaxis (Pavon 2016; Sachdeva 2014). Available evidence about effects of NMES on clinical VTE outcomes compared with pharmacological methods of prophylaxis is inconclusive. Moreover, the additional effectiveness of NMES combined with other methods of VTE prophylaxis remains unknown.

Bleeding was one of the primary outcomes of the current review that was not reported by any of the included trials. Moreover, none of the included trials reported physiological measurements or freedom from VTE at 90 days as an outcome. Poor patient compliance is one of the principal disadvantages of mechanical methods of prophylaxis. None of the included studies reported patient compliance or NMES device-related adverse effects; therefore, it remains unclear whether NMES would result in better compliance in comparison with other methods of mechanical prophylaxis.

Heterogeneity among the included studies did not allow us to define the most effective device and setting for delivery of NMES. Moreover, evidence is insufficient to allow defining a group of patients who can benefit most from NMES as a method of VTE prophylaxis.

Quality of the evidence

See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; and Summary of findings 8.

Overall, the quality of available evidence is low.

Allocation concealment and blinding of participants were inadequate in most of the included trials, subjecting them to high risk of selection and performance bias, respectively. Moreover, included studies show poorly reported blinding of outcome assessment, increasing the likelihood of detection bias. Consequently, the poor reporting and methodological quality of the included trials did not allow us to synthesise robust evidence about the effectiveness of NMES in the prevention of VTE.

For each comparison, a very limited number of studies reported most of the outcomes; therefore, few participants and few events may have led to imprecise effect estimates, reflected by wide confidence intervals for calculated ORs. Moreover, the included studies were heterogeneous in terms of participant populations and settings for delivery of NMES.

Most of the included studies did not contribute to one or more of the primary and secondary outcomes of our review (e.g. bleeding, device-related adverse effects), subjecting the available evidence to some publication bias.

Potential biases in the review process

To minimise the risk of bias in this review, at least two independent review authors were involved in study selection, data extraction, methodological quality assessment, and data analysis. Some bias in the review process may arise, as the results of two ongoing trials were not available; we will include these trials in future updates of this review (ISRCTN95441725; NCT01935414).

Agreements and disagreements with other studies or reviews

In a recent systematic review of 21 randomised and non-randomised studies, we identified conflicting evidence on the effect of

NMES on the incidence of VTE (Hajibandeh 2015). Moreover, among the studies that compared the incidence of DVT in stimulated versus non-stimulated legs in the same participant, some reported a reduction in the incidence of DVT in the stimulated leg (Browse 1970; Doran 1967; Nicolaides 2013), whereas others found no difference in the risk of DVT between legs (Doran 1970). NMES has proved experimentally effective in increasing venous blood velocity and flow; however, controversy exists as to whether venous velocity and flow should be used as surrogate outcome measures for the risk of VTE (Hajibandeh 2015). NMES may prevent VTE via other mechanisms. It has been argued that neuromuscular stimulation of the veins provides direct antithrombotic effects as a fourth factor not included in Virchow's triad; NMES, via neurogenic pathways, may influence this fourth factor and suppress thrombogenesis (Stefanou 2016). This highlights the need for additional studies on the mechanisms of VTE prevention. Although available clinical trials have not reported any outcomes regarding tolerability of NMES, evidence from experimental studies suggests that modern NMES devices appear to be associated with mild pain and discomfort that can potentially lead to good patient compliance (Broderick 2010; Broderick 2013; Moloney 2006; Warwick 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence suggests no clear differences in the risk of deep vein thrombosis (DVT) between neuromuscular electrical stimulation systems (NMES) and alternative methods of prophylaxis, but moderate-quality evidence shows that NMES was associated with lower risk of DVT when compared with no prophylaxis, and low-quality evidence suggests higher risk of DVT when compared with low-dose heparin. The best available evidence on the effectiveness of NMES in the prevention of VTE is not adequately robust to permit definitive conclusions.

Implications for research

Adequately powered high-quality randomised controlled trials are required to provide robust evidence on:

- effectiveness of NMES versus other pharmacological or mechanical methods of VTE prophylaxis;
- additional effects of NMES combined with other methods on VTE prophylaxis;
- cost-effectiveness of NMES in the setting of VTE prophylaxis;
- the most effective device and setting for delivery of NMES; and
- the population that can potentially benefit most from NMES as a method of prophylaxis.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bostrom 1986

Methods	Quasi-randomised case-controlled trial
Participants	Number of participants: 104 (NMES: 46; low-dose heparin: 58) Inclusion criteria: neurosurgical patients aged 40 years or older with normal laboratory coagulation values and operated on under general anaesthesia
Interventions	NMES group: preoperative calf muscle stimulation with groups of impulses, followed by Dextran 70 administered postoperatively. Stimulation characteristics included stimulus strength 40 to 50 mA; impulse duration 50 ms; number of impulses per group 6; impulse frequency within groups 8 per second; group frequency 8 per minute Low-dose heparin group: Heparin (sodium heparin, Heparin, Lrvens, 5000 IU × 2 subcutaneously) was administered 2 hours preoperatively and was continued daily for 1 week postoperatively
Outcomes	DVT (Participants were screened by fibrinogen uptake test; whenever possible, a phlebography was performed.)
Notes	Of 122 participants who entered the study, 18 were excluded during the course of the study. The most common reason for not completing the prophylaxis for the intended full week was early discharge from the hospital. One participant died 5 days after clipping of a ruptured intracranial aneurysm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The participant's year of birth was chosen as a method for randomisation
Allocation concealment (selection bias)	High risk	The study was quasi-randomised, and allocation was not adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants and personnel was reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	US or CT operator/radiologist was not blinded to patient allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 122 participants who entered the study, 18 were excluded during the course of the study. However, the missing outcome data were balanced in numbers across intervention

Bostrom 1986 (*Continued*)

		groups, and reasons for missing data were similar across groups
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	Low risk	None was identified.

Goyal 2012

Methods	Quasi-randomised case-controlled trial
Participants	Number of participants: 200 (NMES: 100; no prophylaxis: 100) Inclusion criteria: patients > 25 years of age requiring surgery around the hip joint who underwent surgery within 2 weeks of sustaining trauma and were operated on under spinal anaesthesia Exclusion criteria: established cases of DVT; taking antithrombotic medication; open fractures; pacemakers; other serious life-threatening conditions, pathological fractures, and associated vascular injuries
Interventions	NMES group: VeinoPlus (Ad Rem Technology, Paris, France) stimulator device for electrostimulation of the calf muscles during surgery. The stimulator device delivered low-voltage (peak value usually around 15 to 25 V) and small-energy impulses (below 25 μC per impulse) to calf muscles Control group: no prophylaxis
Outcomes	DVT (diagnosed by Doppler ultrasound 7 days after surgery)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Participants were randomised into 2 groups of 100 participants each by odd-even number
Allocation concealment (selection bias)	High risk	The study was quasi-randomised, and allocation was not adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The radiologist was blinded about the study and groups of participants

Goyal 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing.
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	Low risk	None was identified.

Hou 2013

Methods	Four-arm randomised controlled trial
Participants	Number of participants: 160 (conventional care group 40; invigorating and promoting Qi group 40; blood-activating and damp-eliminating group 40; acupoint-combination stimulation group 40) Inclusion criteria: age > 60 years; patients who underwent major surgery, including general surgeries, major gynaecological surgeries, limb fracture repairs, etc.; operative duration > 2 hours; patients on postoperative bed rest who could not get out of bed; and patients who signed the informed consent form Exclusion criteria: inability to implement care measures in non-compliant patients; patients who dropped out halfway for various reasons; inability to implement interventions in patients with lower limb infection; and inability to implement interventions among patients in critical condition
Interventions	Invigorating and promoting Qi group: postoperative routine care plus bilateral transcutaneous electrical stimulation at Taichong (LR 3) and Zusanli (ST 36) in two 20-minute sessions per day (morning and afternoon) for 1 week Blood-activating and damp-eliminating group: postoperative routine care plus bilateral transcutaneous electrical stimulation at Yinlingquan (SP 9) and Sanyinjiao (SP 6) in two 20-minute sessions per day (morning and afternoon) for 1 week Acupoint-combination stimulation group: postoperative routine care plus bilateral transcutaneous electrical stimulation at a combination of 4 acupoints: Taichong (LR 3), Zusanli (ST 36), Yinlingquan (SP 9), and Sanyinjiao (SP 6), in two 20-minute sessions per day (morning and afternoon) for 1 week Conventional care group: postoperative routine care, including observation, basic care, catheter care, prevention and care of complications, and health education. In addition, participants received help with raising the lower extremities and were given postoperative symptomatic care
Outcomes	DVT (diagnosed by Doppler ultrasound 7 days after surgery) D-dimer levels Changes in haemorheology: blood viscosity (including whole blood viscosity and plasma viscosity)
Notes	Data for the 3 NMES groups were combined in analyses.
Risk of bias	

Hou 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random numbers table was used.
Allocation concealment (selection bias)	Unclear risk	This was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing.
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	High risk	The study was Industry sponsored.

Kiudelis 2002

Methods	Three-arm randomised controlled trial
Participants	Number of participants: 54 (NMES group 18; GCS group 18; IPCD group 18) Inclusion criteria: adult patients undergoing elective laparoscopic fundoplication Exclusion criteria: not reported
Interventions	NMES group: intermittent electrical calf muscle stimulation during operation GCS group: GCS during operation IPCD group: IPCD during operation
Outcomes	Lower extremity venous blood velocity (measured by Doppler ultrasonography during operation) DVT (1 day after operation using venous occlusion plethysmography) PE (1 day after operation using lung perfusion scintigraphy)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Kiudelis 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Unclear risk	This was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing.
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	Low risk	None was identified.

Lindstrom 1982

Methods	Three-arm randomised controlled trial
Participants	Number of participants: 112 (stimulation group 37; control group 40; Dextran 40 group 35) Inclusion criteria: patients who underwent major abdominal surgery
Interventions	Stimulation group: optimised bilateral calf muscle stimulation with groups of impulses during the entire operation.(strength 40 to 50 mA, impulse duration 50 ms; number of impulses per group 6; impulse frequency within group 8 amp/s; group frequency 8 groups/min) Control group: standard routine of the ward. Plasma and whole blood were given to replace blood lost Dextran 40 group: 500 mL Dextran 40 was given perioperatively and during the first and third postoperative days
Outcomes	DVT (Participants were screened by fibrinogen uptake test; whenever possible, a phlebography was performed.) PE (diagnosed by pulmonary perfusion scintigraphy) Total VTE PE with DVT
Notes	
Risk of bias	

Lindstrom 1982 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Unclear risk	This was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing.
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	Low risk	None was identified.

Merli 1988

Methods	Three-arm randomised controlled trial
Participants	Number of participants: 48 (NMES + low-dose heparin group 15; low-dose heparin group 16; saline placebo group 17) Inclusion criteria: patients with C2 to T11 motor complete and incomplete, preserved motor, non-functional spinal cord injuries
Interventions	NMES + low-dose heparin group: Tibialis anterior and gastrocnemius-soleus muscle groups were stimulated bilaterally via 50-microsecond pulses given at 10 Hz with a 4-second "on" and 8-second "off" cycle for 23 hours daily over a 28-day period + 5000 IU heparin, given subcutaneously every 8 hours Low-dose heparin group: 5000 IU heparin, given subcutaneously every 8 hours Placebo: saline
Outcomes	DVT (Venography was performed to confirm positive impedance plethysmography and/or fibrinogen uptake tests.)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Merli 1988 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Data about randomisation were not reported.
Allocation concealment (selection bias)	Unclear risk	This was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants in control group received placebo saline.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes were reported.
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	Low risk	None was identified.

Rosenberg 1975

Methods	Quasi-randomised case-controlled trial
Participants	Number of participants: 194 (NMES group 50; no prophylaxis group 89; low-dose heparin group 55) Inclusion criteria: Patients older than 40 years undergoing a major general surgical operation for which they were expected to be in hospital for at least a week were eligible to enter the trial Exclusion criteria: No exclusions were made on the grounds of pre-existing cardiorespiratory disease, peripheral vascular disease, or varicose veins; or previous history of thrombosis; but for technical reasons patients undergoing thyroidectomy, left mastectomy, and peripheral arterial reconstruction were not studied
Interventions	NMES group: intermittent electrical calf muscle stimulation during surgery, use of Thrombophylactor (Rank Precision Industries Ltd., Maidenhead, Berkshire, UK), which delivers an interrupted direct current of 50 milliseconds duration every 5 seconds Low-dose heparin group: heparin calcium administered subcutaneously 5000 IU, the first dose 2 hours before operation, then every 8 hours until the end of the sixth postoperative day, or until the participant was fully mobile, whichever was longer No prophylaxis group: leg exercises only
Outcomes	DVT (The fibrinogen uptake test was performed on all participants for diagnosis.)
Notes	

Rosenberg 1975 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation into 3 groups was by month of birth.
Allocation concealment (selection bias)	High risk	The study was a quasi-randomised trial, and allocation was not adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing.
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	High risk	This study was industry sponsored.

Velmahos 2005

Methods	Two-arm randomised controlled trial
Participants	Number of participants: 47 (NMES group 26; non-NMES group 21) Inclusion criteria: trauma patients with Injury Severity Score > 9 who were admitted to the intensive care unit and had a contraindication for prophylactic heparin; significant head injury; operation for extensive organ injury; major retroperitoneal haematoma; liver, spleen, or kidney injury higher than Grade II, managed non-operatively; other injuries that at the discretion of the trauma surgeon were deemed to be associated with a high likelihood for bleeding; anticipated survival for longer than 7 days; anticipated hospital stay longer than 7 days; and randomisation within 24 hours of injury Exclusion criteria: younger than 18 years; known allergy to contrast material, precluding use of venography, cardiac demand pacemakers, or other implanted stimulators or implants containing metal parts within the area of treatment; spastic paralysis; local infection at the site of application; and history or present evidence of venous thrombosis. Trauma to the extremity was not an exclusion criterion
Interventions	NMES group: two 30-minute sessions daily, 1 in the morning and 1 in the evening, using the Lymphavision stimulator (Physiomed Elektromedizin AG, Schnaittach, Germany) . Voltage was applied gradually (0 to 120 V) to obtain a slightly visible twitch of the

	muscles. Stimuli 3 milliseconds long were used at a frequency of 1.75 Hz (105/min) with inversion of polarity every 5 seconds Non-NMES group: managed according to standard of care with no thromboprophylaxis for as long as contraindications existed Participants in both groups were allowed to have standard prophylaxis with subcutaneous unfractionated or LMWH when the contraindication for its use was no longer present
Outcomes	DVT (diagnosed by venography or Doppler ultrasound) Venous blood flow velocity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Type and method of randomisation are not clearly described.
Allocation concealment (selection bias)	Unclear risk	Type and method of randomisation are not clearly described, and allocation concealment cannot be judged confidently
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data were not balanced in numbers across intervention groups: 4 NMES and 9 control participants were excluded from analysis because of lack of outcome evaluation (2 control participants died, 7 control participants and 1 NMES participant were transferred to another hospital, and 2 NMES participants refused to continue the study despite initial consent)
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that published reports include all expected outcomes
Other bias	High risk	The study was industry sponsored.

CT: computed tomography.

DVT: deep vein thrombosis.
GCS: graduated compression stockings.
IPCD: intermittent pneumatic compression devices.
LMWH: low molecular weight heparin.
ms: milliseconds.
NMES: neuromuscular electrical stimulation.
PE: pulmonary embolism.
US: ultrasound.
VTE: venous thromboembolism.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Browse 1970	Randomised legs instead of participants
Czyrny 2010	Included healthy individuals
Doran 1967	Randomised legs instead of participants
Doran 1970	Randomised legs instead of participants
Faghri 1998	Non-randomised, non-clinical study
Hou 2014	Study did not report outcomes defined in our review paper. Study authors were contacted to clarify if any of our review outcomes had been measured, but no reply was received
Izumi 2014	Only 1 leg received NMES; the other leg received other methods of thromboprophylaxis
Jansen 1972	Investigated non-mechanical methods of prophylaxis
Kaplan 2002	Included healthy individuals
Lobastov 2014	Non-randomised study
Morita 2006	Included healthy individuals
NCT02425917	Trial was withdrawn before enrolment.
Nicolaides 1983	Randomised legs instead of participants
Ojima 2017	Investigated haemodynamic outcomes and was powered for these outcomes only
Pambianco 1995	NMES arm was terminated early in the pilot phase.
Rosengarten 1975	Investigated non-mechanical methods of prophylaxis

(*Continued*)

Yilmaz 2016	Investigated haemodynamic outcomes only

NMES: neuromuscular electrical stimulation.

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01835990

Methods	Two-arm randomised controlled trial
Participants	Inclusion criteria: diagnosis of trauma; age 18 years or older; contraindication to anticoagulation expected to last longer than 3 days; projected hospitalisation longer than 3 days; and informed consent Exclusion criteria: inability to wear either IPCs or geko™ (Sky Medical Technology Ltd, Newport, Vermont, USA) on both legs; diagnosis of DVT within 1 month before assessment for enrolment; use of anticoagulant medication within 24 hours of enrolment; leg circumference greater than 24 inches at the location where the geko™ device would be secured to the leg; or presence of cardiac demand pacemaker
Interventions	Intervention group: geko™ Comparator group: IPCs
Outcomes	Incidence of DVT Compliance VTE Tolerability Venous and arterial physiological flow
Notes	Study has been completed. Results of this study are not yet available

DVT: deep vein thrombosis.
IPC: intermittent pneumatic compression device.
VTE: venous thromboembolism.

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN95441725

Trial name or title	Does the Geko™ nerve stimulator reduce deep vein thrombosis (DVT) and improve healing in ankle fractures?
Methods	Randomised controlled trial
Participants	Adults aged 18 years or older, either sex, with closed ankle fractures that have required open reduction and internal fixation; able to consent for themselves

ISRCTN95441725 (*Continued*)

Interventions	Each participant randomised into 1 of 2 groups, i.e. those who receive the stimulator for a 2-week period postoperatively and those who do not
Outcomes	DVT rate; time to union
Starting date	01/11/2012
Contact information	Wirral University Teaching Hospital
Notes	The study has been completed, but results have not yet been published. Study authors contacted, but no reply

NCT01935414

Trial name or title	Geko™ neuromuscular stimulator vs thromboembolism deterrent stockings (TEDS): DVT prevention study
Methods	Open-label randomised controlled trial
Participants	Inclusion criteria: aged 18 years or older; free of significant abnormal findings as determined by medical history (specifically, absence of DVT or haematological disorders); no reported use of 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; and able and willing to follow the protocol requirements
Interventions	Intervention: continual Geko™ use post surgery for 48 hours, then for a minimum of 4 hours/d until discharge Control: continual use of TEDS stockings post surgery for 48 hours, then for a minimum of 4 hours/d until discharge
Outcomes	Presence of asymptomatic DVT assessed by duplex ultrasound
Starting date	August 2013
Contact information	matthew.womack@firstkindmedical.com
Notes	

DVT: deep vein thrombosis.
NMES: neuromuscular electrical stimulation.
TEDS: thromboembolism deterrent stockings.

DATA AND ANALYSES

Comparison 1. NMES versus alternative prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	6	415	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.60, 1.70]
2 Asymptomatic DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Symptomatic DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 PE	2	126	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.38, 4.48]
5 Total VTE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. NMES versus no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	4	576	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.23, 0.70]
2 Asymptomatic DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Symptomatic DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 PE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Total VTE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. NMES versus low-dose heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	2	194	Odds Ratio (M-H, Fixed, 95% CI)	2.78 [1.19, 6.48]
2 Asymptomatic DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Symptomatic DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. NMES versus Dextran 40

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 PE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Total VTE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Combined NMES and low-dose heparin versus no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 6. Combined NMES and low-dose heparin versus low-dose heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. NMES versus GCS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 PE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 8. NMES versus IPCD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total DVT	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 PE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 NMES versus alternative prophylaxis, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 1 NMES versus alternative prophylaxis

Outcome: 1 Total DVT

Study or subgroup	NMES n/N	Alternative methods n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Rosenberg 1975	14/50	4/55		9.8 %	4.96 [1.51, 16.30]
Lindstrom 1982	5/37	7/35		22.2 %	0.63 [0.18, 2.19]
Bostrom 1986	5/40	5/49		14.0 %	1.26 [0.34, 4.69]
Merli 1988	1/15	16/33		33.2 %	0.08 [0.01, 0.65]
Kiudelis 2002	0/18	1/36		3.5 %	0.64 [0.02, 16.49]
Velmahos 2005	7/26	6/21		17.3 %	0.92 [0.26, 3.32]
Total (95% CI)	**186**	**229**		**100.0 %**	**1.01 [0.60, 1.70]**

Total events: 32 (NMES), 39 (Alternative methods)

Heterogeneity: Chi^2 = 13.25, df = 5 (P = 0.02); I^2 =62%

Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable

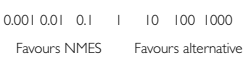
Analysis 1.2. Comparison 1 NMES versus alternative prophylaxis, Outcome 2 Asymptomatic DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 1 NMES versus alternative prophylaxis

Outcome: 2 Asymptomatic DVT

Study or subgroup	NMES n/N	Alternative methods n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Bostrom 1986	5/40	4/49		1.61 [0.40, 6.43]



Analysis 1.3. Comparison 1 NMES versus alternative prophylaxis, Outcome 3 Symptomatic DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 1 NMES versus alternative prophylaxis

Outcome: 3 Symptomatic DVT

Study or subgroup	NMES n/N	Alternative methods n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Bostrom 1986	0/40	1/49		0.40 [0.02, 10.07]

Analysis 1.4. Comparison 1 NMES versus alternative prophylaxis, Outcome 4 PE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 1 NMES versus alternative prophylaxis

Outcome: 4 PE

Study or subgroup	NMES n/N	Alternative methods n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Lindstrom 1982	6/37	4/35		77.7 %	1.50 [0.39, 5.84]
Kiudelis 2002	0/18	1/36		22.3 %	0.64 [0.02, 16.49]
Total (95% CI)	**55**	**71**		**100.0 %**	**1.31 [0.38, 4.48]**

Total events: 6 (NMES), 5 (Alternative methods)

Heterogeneity: $Chi^2 = 0.23$, df = 1 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 NMES versus alternative prophylaxis, Outcome 5 Total VTE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 1 NMES versus alternative prophylaxis

Outcome: 5 Total VTE

Study or subgroup	NMES n/N	Alternative methods n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Lindstrom 1982	11/37	11/35		0.92 [0.34, 2.52]

Analysis 2.1. Comparison 2 NMES versus no prophylaxis, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 2 NMES versus no prophylaxis

Outcome: 1 Total DVT

Study or subgroup	NMES n/N	No prophylaxis n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Rosenberg 1975	14/50	39/89		50.8 %	0.50 [0.24, 1.05]
Lindstrom 1982	5/37	12/40		25.1 %	0.36 [0.11, 1.16]
Goyal 2012	2/100	6/100		14.8 %	0.32 [0.06, 1.62]
Hou 2013	0/120	2/40		9.4 %	0.06 [0.00, 1.36]
Total (95% CI)	**307**	**269**		**100.0 %**	**0.40 [0.23, 0.70]**

Total events: 21 (NMES), 59 (No prophylaxis)

Heterogeneity: Chi^2 = 1.82, df = 3 (P = 0.61); I^2 =0.0%

Test for overall effect: Z = 3.18 (P = 0.0015)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 NMES versus no prophylaxis, Outcome 2 Asymptomatic DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 2 NMES versus no prophylaxis

Outcome: 2 Asymptomatic DVT

Study or subgroup	NMES n/N	No prophylaxis n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Goyal 2012	2/100	6/100		0.32 [0.06, 1.62]

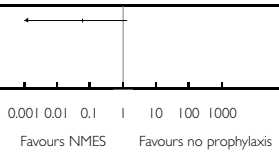
Analysis 2.3. Comparison 2 NMES versus no prophylaxis, Outcome 3 Symptomatic DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 2 NMES versus no prophylaxis

Outcome: 3 Symptomatic DVT

Study or subgroup	NMES n/N	No prophylaxis n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Hou 2013	0/120	2/40		0.06 [0.00, 1.36]



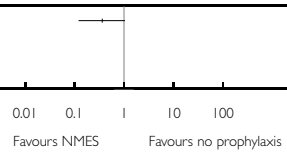
Analysis 2.4. Comparison 2 NMES versus no prophylaxis, Outcome 4 PE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 2 NMES versus no prophylaxis

Outcome: 4 PE

Study or subgroup	NMES n/N	No prophylaxis n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Lindstrom 1982	6/37	14/40		0.36 [0.12, 1.07]

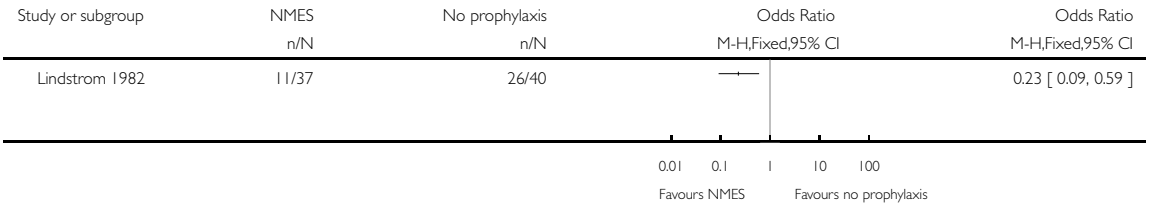


Analysis 2.5. Comparison 2 NMES versus no prophylaxis, Outcome 5 Total VTE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 2 NMES versus no prophylaxis

Outcome: 5 Total VTE

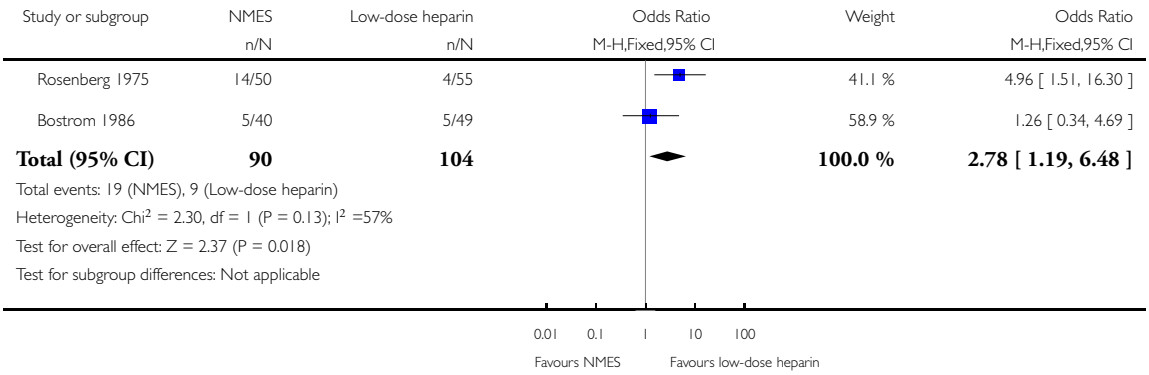


Analysis 3.1. Comparison 3 NMES versus low-dose heparin, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 3 NMES versus low-dose heparin

Outcome: 1 Total DVT



Analysis 3.2. Comparison 3 NMES versus low-dose heparin, Outcome 2 Asymptomatic DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 3 NMES versus low-dose heparin

Outcome: 2 Asymptomatic DVT

Study or subgroup	NMES n/N	Low-dose heparin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Bostrom 1986	5/40	4/49		1.61 [0.40, 6.43]

Analysis 3.3. Comparison 3 NMES versus low-dose heparin, Outcome 3 Symptomatic DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 3 NMES versus low-dose heparin

Outcome: 3 Symptomatic DVT

Study or subgroup	NMES n/N	Low-dose heparin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Bostrom 1986	0/40	1/49		0.40 [0.02, 10.07]

Analysis 4.1. Comparison 4 NMES versus Dextran 40, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 4 NMES versus Dextran 40

Outcome: 1 Total DVT

Study or subgroup	NMES n/N	Dextran 40 n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Lindstrom 1982	5/37	7/35		0.63 [0.18, 2.19]

Analysis 4.2. Comparison 4 NMES versus Dextran 40, Outcome 2 PE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 4 NMES versus Dextran 40

Outcome: 2 PE

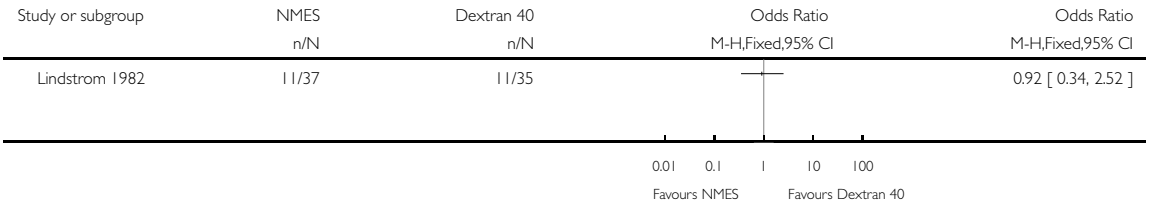
Study or subgroup	NMES n/N	Dextran 40 n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Lindstrom 1982	6/37	4/35		1.50 [0.39, 5.84]

Analysis 4.3. Comparison 4 NMES versus Dextran 40, Outcome 3 Total VTE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 4 NMES versus Dextran 40

Outcome: 3 Total VTE

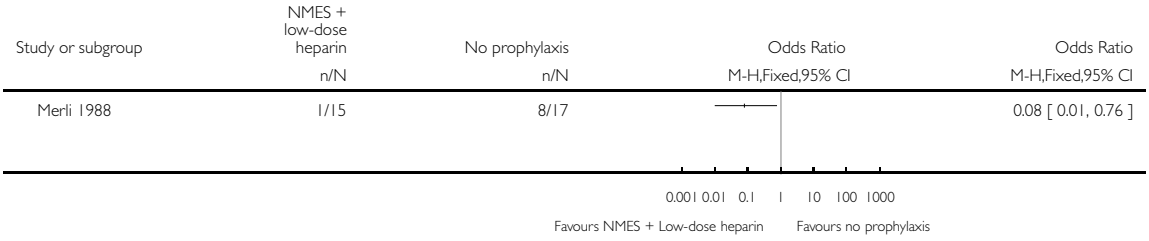


Analysis 5.1. Comparison 5 Combined NMES and low-dose heparin versus no prophylaxis, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 5 Combined NMES and low-dose heparin versus no prophylaxis

Outcome: 1 Total DVT

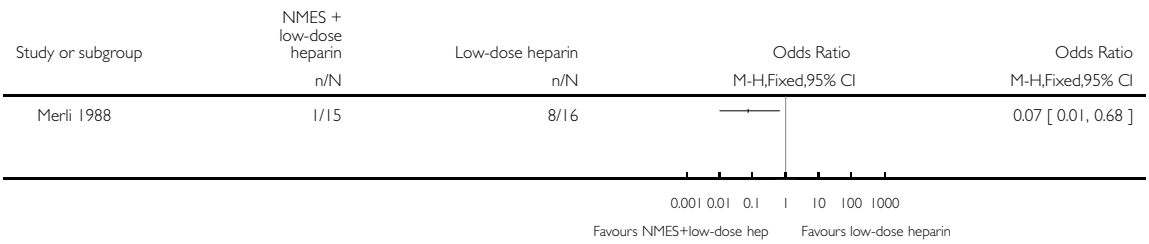


Analysis 6.1. Comparison 6 Combined NMES and low-dose heparin versus low-dose heparin, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 6 Combined NMES and low-dose heparin versus low-dose heparin

Outcome: 1 Total DVT

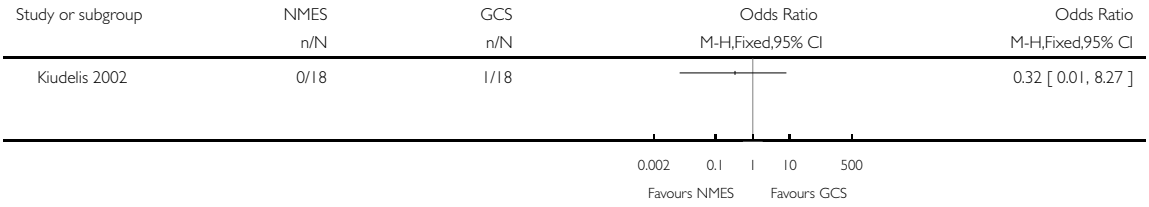


Analysis 7.1. Comparison 7 NMES versus GCS, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 7 NMES versus GCS

Outcome: 1 Total DVT

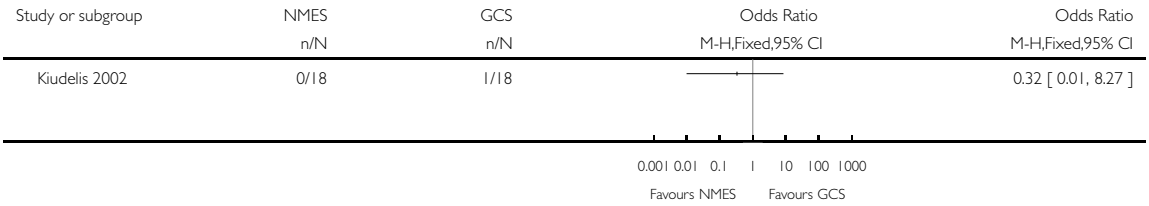


Analysis 7.2. Comparison 7 NMES versus GCS, Outcome 2 PE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 7 NMES versus GCS

Outcome: 2 PE

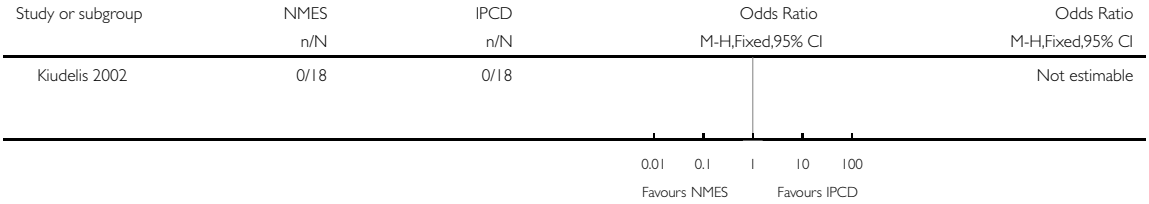


Analysis 8.1. Comparison 8 NMES versus IPCD, Outcome 1 Total DVT.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 8 NMES versus IPCD

Outcome: 1 Total DVT

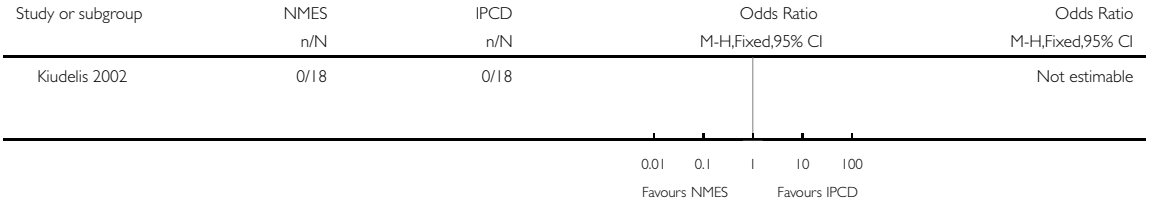


Analysis 8.2. Comparison 8 NMES versus IPCD, Outcome 2 PE.

Review: Neuromuscular electrical stimulation for the prevention of venous thromboembolism

Comparison: 8 NMES versus IPCD

Outcome: 2 PE



ADDITIONAL TABLES

Table 1. Neuromuscular electrical stimulation delivery in the included studies

Study	Device	Frequency (Hz)	Pulse width	Charge (mA)	Voltage (V)	Duration
Hou 2013	G6805-II	30-100	NR	NR	6-15	7 days (20 minutes twice/d)
Goyal 2012	VEINOPLUS	NR	NR	NR	15-25	Only during surgery
Velmahos 2005	Lymphavision	1.75	3 ms	NR	0-120	7-14 days (30 minutes twice/d)
Kiudelis 2002	Mioritm 021	NR	NR	50-100	NR	Only during surgery
Merli 1988	NR	10	50 μs	NR	NR	28 days (23 hours/d)
Bostrom 1986	NR	8	50 ms	40-50	NR	7 days
Lindstrom 1982	NR	8	50 ms	40-50	NR	Only during surgery
Rosenberg 1975	Thrombophy-lactor	NR	50 ms	NR	Adjustable	Only during surgery

NR: rot reported.

APPENDICES

Appendix 1. Glossary of terms for lay readers

Terms	Meaning
Anticoagulant	Having the effect of retarding or inhibiting the coagulation or clotting of blood. Anticoagulants are a class of drugs that work to prevent coagulation of blood
Compliance	The action or fact of complying with treatment
Deep vein thrombosis (DVT)	Formation of a blood clot in a deep vein - usually in the leg or pelvic veins
Endothelium	The tissue that forms a single layer of cells lining various organs and cavities of the body, especially the blood vessels, heart, and lymphatic vessels
Factor V Leiden	A mutation of one of the clotting factors in the blood called factor V. This mutation can increase the chance of developing abnormal blood clots (thrombophilia), usually in the veins
Graduated compression stockings (GCS)	Elastic garments worn around the leg, compressing the limb. They help to prevent the occurrence or further progression of venous disorders such as oedema, phlebitis, and thrombosis
Hypercoagulable state	An abnormality of blood coagulation that increases the risk of thrombosis
Incidence	The occurrence, rate, or frequency of a disease
Intermittent pneumatic compression devices (IPCD)	A therapeutic technique used in medical devices that include an air pump and inflatable auxiliary sleeves, gloves, or boots in a system designed to improve venous circulation in the limbs of patients who suffer oedema or risk of DVT or PE
Malignancy	The state or presence of a malignant tumour; cancer
Morbidity	The frequency of complications resulting from treatment or disease
Mortality	The frequency of death resulting from treatment or disease
Neuromuscular electrical stimulation (NMES)	Delivery of electrical impulses via electrodes to the skin over selected muscle groups or nerves to induce an involuntary muscle contraction
Oedema	Fluid retention in the body
Paraplagia	Paralysis of the legs and lower body, typically caused by spinal injury or disease
Pathogenesis	The manner of development of a disease

(*Continued*)

Pharmacology	The science of drugs including their origin, composition, pharmacokinetics, therapeutic use, and toxicology
Prophylaxis	Treatment given or action taken to prevent disease
Pulmonary embolism (PE)	A sudden blockage in a lung artery that is caused by a blood clot that travels to the lung from a vein in the leg
Subcutaneous	Situated or applied under the skin
Thrombophilia	An abnormal tendency to develop blood clots
Thrombosis	Blood clots in blood vessels
Venous thromboembolism	The occurrence DVT or PE or both

Appendix 2. CENTRAL search strategy

#1	MESH DESCRIPTOR Electric Stimulation EXPLODE ALL TREES	1788
#2	(neuromusc* near3 stimul*):TI,AB,KY	495
#3	(electr* near3 stimul*):TI,AB,KY	7108
#4	(musc* near3 stimul*):TI,AB,KY	711
#5	(calf* near3 stimul*):TI,AB,KY	18
#6	(foot* near3 stimul*):TI,AB,KY	47
#7	(lower near3 stimul*):TI,AB,KY	168
#8	(limb near3 stimul*):TI,AB,KY	52
#9	(peroneal near3 stimul*):TI,AB,KY	37
#10	electromyostimul*:TI,AB,KY	66
#11	NMES:TI,AB,KY	242
#12	geko*:TI,AB,KY	8
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	7873

(*Continued*)

#14	MESH DESCRIPTOR Thrombosis	1267
#15	MESH DESCRIPTOR Thromboembolism	921
#16	MESH DESCRIPTOR Venous Thromboembolism	258
#17	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES	2041
#18	(thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):TI,AB,KY	18996
#19	MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES	748
#20	(PE or DVT or VTE):TI,AB,KY	4988
#21	((vein* or ven*) near thromb*):TI,AB,KY	6717
#22	(blood near3 clot*):TI,AB,KY	2966
#23	(pulmonary near3 clot*):TI,AB,KY	5
#24	(lung near3 clot*):TI,AB,KY	4
#25	(venous near3 stasis):TI,AB,KY	128
#26	(venous near3 empty*):TI,AB,KY	10
#27	(blood near3 stasis):TI,AB,KY	453
#28	(blood near3 supply):TI,AB,KY	7412
#29	MESH DESCRIPTOR Hemodynamics EXPLODE ALL TREES	46548
#30	MESH DESCRIPTOR Lower Extremity EXPLODE ALL TREES WITH QUALIFIERS BS	1521
#31	(blood near3 flow):TI,AB,KY	12698
#32	hemodynamic*:TI,AB,KY	21594
#33	haemodynamic*:TI,AB,KY	5411
#34	fibrinoly*:TI,AB,KY	4822

(*Continued*)

#35	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	93374
#36	#13 AND #35	709

CONTRIBUTIONS OF AUTHORS

Shahab H: design and writing of the protocol and review, final approval of the protocol and review.

Shahin H: design and writing of the protocol and review, final approval of the protocol and review.

GA: conception, critical review, revision, and final approval of the protocol and review.

JS: conception, critical review, revision, and final approval of the protocol and review.

FT: conception, critical review, revision, and final approval of the protocol and review.

DECLARATIONS OF INTEREST

Shahab H: none known.

Shahin H: none known.

GA: none known.

JS: none known.

FT declares that he has received educational sponsorship (travel, accommodation, and meeting-related expenses) from Endologix Inc. Endologix Inc. produces medical devices that are not used for treatment of venous disease and bear no direct relevance to the topic of this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For completeness, we added the comparison of NMES versus no prophylaxis. Also, we considered ICU patients in the subgroup analysis section.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [therapeutic use]; Contraindications, Drug; Dextrans [therapeutic use]; Electric Stimulation Therapy [*methods]; Heparin [therapeutic use]; Intermittent Pneumatic Compression Devices; Neuromuscular Junction; Postthrombotic Syndrome [prevention & control]; Randomized Controlled Trials as Topic; Stockings, Compression; Venous Thromboembolism [prevention & control]; Venous Thrombosis [*prevention & control]

MeSH check words

Humans