Effects and safety of intraoperative intermittent pneumatic compression for preventing postoperative venous thromboembolism: a meta-analysis

Type
Research paper

Keywords
surgery, prevention, venous thromboembolism, care, intermittent pneumatic compression

Abstract
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Intermittent pneumatic compression (IPC) has been used for venous thrombosis (VTE) prevention. It's necessary to evaluate the effects and safety of intraoperative use of IPC devices in the prevention of VTE in surgical patients.

Material and methods
Two authors independently searched the PubMed, Cochrane Library, MedLine, EMBase, China national knowledge infrastructure (CNKI), Wanfang databases for randomized controlled trials (RCTs) and cohort studies on the use of IPC in surgical patients up to June 10, 2021. The Cochrane Collaborations risk of bias tool and Newcastle-Ottawa Scale (NOS) were used for quality assessment. RevMan 5.3 software were used for statistical analyses.

Results
A total of 13 studies including seven RCTs and six retrospective cohort studies involving 6673 surgical patients were included, 1883 patients underwent IPC intervention. The synthesized RCT results indicated that IPC was beneficial to the reduce the incidence of DVT (RR0.30, 95%CI0.22~0.40, P<0.001) and VTE (RR0.51, 95%CI0.27~0.95, P=0.03). The synthesized results from retrospective cohort studies indicated that IPC is beneficial to the reduce the incidence of DVT (RR0.63, 95%CI0.42~0.96, P=0.03) and PE (RR0.34, 95%CI0.16~0.72, P=0.005). No significant publication biases were found for all synthesized outcomes (all p>0.05).

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IPC seems to be safe and effective in the prevention and management of intraoperative VTE. Limited by sample size, this conclusion still needs to be further confirmed by large-sample, multi-center, high-quality clinical studies.
Title: Effects and safety of intraoperative intermittent pneumatic compression for preventing postoperative venous thromboembolism: a meta-analysis

Running title: intermittent pneumatic compression & VTE

Authors: Yanping Yang¹, Jianhua Li²¹

¹, Department of nursing, The First People’s Hospital of Lianyungang, The Affiliated Lianyungang Hospital of Xuzhou Medical University, Jiangsu, China

²¹, Corresponding author

Corresponding to: Jianhua Li yzecsk385172@163.com

Address: No. 182, Tongyu North Road, Haizhou District, Lianyungang, Jiangsu Province, China.

Telephone: 12815194604

Fax: 0024 0681 1026
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Background

Venous thromboembolism (VTE) is a common yet potentially life-threatening complication during the perioperative period, including deep vein thrombosis (DVT) and pulmonary embolism (PE). According to previous reports[1, 2], there are more than 698,000 cases of symptomatic DVT and more than 434,000 cases of PE in Europe each year, resulting in more than 543,000 deaths. The incidence of VTE events in Asia is lower than that in European countries[3]. However, with the development of medical diagnosis methods and the strengthening of population awareness, the incidence of VTE is increasing year by year[4, 5]. When a patient presents with DVT, the main manifestations are lower extremity swelling, pain, superficial vein dilation, elevated skin temperature, and restricted activity[6]. If not diagnosed and treated in time, fatal PE may occur, manifested as chest pain, cough, and dyspnea or even death[7]. Therefore, the prevention and treatment of VTE has become a major health problem of global medical workers.

The prevention and treatment of VTE in the perioperative period is of great significance to the prognosis of surgical patients. Intermittent pneumatic compression (IPC) is a device that uses mechanical inflation to compress the veins of the lower limbs to promote blood circulation[8]. Several clinical studies[7, 9] have shown that IPC is beneficial to reduce the occurrence of perioperative VTE, promote rapid perioperative recovery, improve the quality of life, and reduce unexpected mortality. However, IPC is currently not widely used in surgery, and due to the limited sample size and different populations, the conclusions drawn by previous studies are different and
inconsistent[10, 11]. Therefore, it’s necessary to evaluate the preventive effect of IPC on perioperative VTE by using the method of meta-analysis, to provide evidence-based basis for the prevention and treatment of VTE in patients during operation.

Methods

We aimed to perform and report this systematic review and meta-analysis in comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12].

Study search

We searched for randomized controlled trials (RCTs) and cohort studies related to the use of IPC in surgical patients, in databases including PubMed, Cochrane Library, MedLine, EMbase, China national knowledge infrastructure (CNKI), Wanfang. The search strategies were ((intermittent pneumatic compression) OR (IPC) OR (mechanical compression)) AND (intraoperative) OR(surgery) OR (operation)) AND ((venous thrombosis) OR (thromboembolism) OR (deep vein thrombosis) OR (DVT) OR (VTE)). The search time limit is from the establishment of the database to June 10, 2021. The languages of reports were limited to Chinese and English. Besides, we checked and reviewed the reference lists of associated RCTs and reviews to avoid any missing reports.

Literature inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were as following: The type of study was RCT or retrospective cohort study on the application of IPC to patients undergoing surgery treatment. The populations of the study were patients ≥18 years of age. The intervention measures covered IPC and the control group, and the cycle and duration of IPC intervention were not limited. The article reported relevant outcome indicators such as the incidence of DVT and PE. The exclusion criteria
for this meta-analysis were as following: case reports, reviews, and observational studies were excluded; related data were incomplete or could not be obtained from contacting the corresponding authors of reports.

Data extraction

Two researchers independently read and screened the literature according to the inclusion and exclusion criteria. When the opinions were inconsistent, we discussed for consents or the third researcher decided whether to include. The content of the literature extraction included the setting, population, sample size, sampling and grouping methods, intervention measures, relevant outcome indicators and research conclusions.

Quality assessment of included studies

The Cochrane Collaborations risk of bias tool[13] was adopted by two authors independently to evaluate the quality and risk of bias of the included RCTs. Seven specific domains were examined in this tool, including: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other issues. Each domain was rated as low risk of bias, high risk of bias or unclear risk of bias according to the judgment criteria. Any disagreements were resolved by discussion and consensus.

In addition, we used the Newcastle-Ottawa Scale (NOS)[14] to evaluate the study quality of the cohort study. The scale included 8 items with a maximum score of 9. The higher the score, the higher the quality of the study.

Statistical analysis

All the statistical analyses were conducted with RevMan 5.3 software. In this present meta-analyses, Binary outcomes were presented as Mantel–Haenszel-style risk ratios(RR) with 95% confidence
intervals (CI). Continuous outcomes were reported as mean differences (MDs). A fixed-effect model was applied in the cases of homogeneity ($P$ value of $\chi^2$ test $>0.1$ and $I^2 < 50\%$), whereas a random-effect model was used in the cases of obvious heterogeneity ($P$ value of $\chi^2$ test $<0.1$ and $I^2 \geq 50\%$).

Publication bias were evaluated by using funnel plots, and asymmetry was assessed by Egger regression test. In this study, $P<0.05$ was considered as the significant difference between groups.

**Results**

**Study selection**

The flow chart of study selection was shown in Figure 1. The initial search identified 128 potentially relevant reports. Of these identified articles, 10 studies were excluded as duplicates. After viewing the titles and abstracts of the 118 remaining studies, the full texts of 41 reports were retrieved. Among them, 28 reports were excluded with failure to meet the inclusion criteria. Finally, a total of 13 studies [15-27] including seven RCTs [15, 16, 21, 22, 25-27] and six retrospective cohort studies [17-20, 23, 24] were included in this meta-analyses.

![Figure 1 PRISMA flow diagram](image)

The characteristics and quality of included studies

As presented in Table 1, of the included 13 studies [15-27] in this meta-analysis, a total of 6673 surgical patients were included, and 1883 patients underwent IPC intervention. The types of surgery included joint replacement, neurosurgery, intracranial surgery, breast surgery, gastrointestinal surgery, gynecological surgery in this meta-analysis. As shown in Table 2 and Table 3, the quality of the studies included in this meta-analysis were generally good. All studies described and
compared baseline data such as age and gender of the two groups of patients, the baseline data between groups were relatively comparable.

Table 1 The characteristics of included RCTs

Table 2 The quality assessment of included RCTs

Table 3 The NOS quality evaluation of included retrospective cohort study

Meta-analysis

The incidence of DVT in the included RCTs 7 RCTs[15, 16, 21, 22, 25-27] reported the incidence of DVT, there was no significant heterogeneity ($I^2=40\%, P=0.13$) and fixed model was applied for meta-analysis. As presented in Figure 2, the synthesize outcome indicated that IPC was beneficial to the reduce the incidence of DVT (RR0.30, 95%CI0.22~0.40, $P<0.001$).

Figure 2 Forest plot for the incidence of DVT in the included RCTs

The incidence of VTE in the included RCTs 5 RCTs[15, 16, 21, 26, 27] reported the incidence of VTE, there was significant heterogeneity ($I^2=61\%, P=0.04$) and random model was applied for meta-analysis. As presented in Figure 3, the synthesize outcome indicated that IPC was beneficial to the reduce the incidence of VTE (RR0.51, 95%CI0.27~0.95, $P=0.03$).

Figure 3 Forest plot for the incidence of VTE in the included RCTs
The incidence of DVT in the included retrospective cohort studies. 6 retrospective cohort studies [17-21, 23, 24] reported the incidence of DVT, there was no significant heterogeneity (I^2=28%, P=0.23) and fixed model was applied for meta-analysis. As presented in Figure 4, the synthesize outcome indicated that IPC was beneficial to the reduce the incidence of DVT (RR 0.63, 95%CI 0.42–0.96, P=0.03).

Figure 4 Forest plot for the incidence of DVT in the included retrospective cohort studies.

The incidence of PE in the included retrospective cohort studies. 3 retrospective cohort studies [18-20] reported the incidence of PE, there was no significant heterogeneity (I^2=0%, P=0.89) and fixed model was applied for meta-analysis. As presented in Figure 5, the synthesize outcome indicated that IPC was beneficial to the reduce the incidence of PE (RR 0.34, 95%CI 0.16–0.72, P=0.005).

Figure 5 Forest plot for the incidence of PE in the included retrospective cohort studies.

Publication bias

As presented in Figure 6, the dots were evenly distributed in the funnel plots for synthesized outcomes, and Egger regression tests indicated that there was no significant publication bias for all synthesized outcomes (all p>0.05).

Figure 6 Funnel plots for synthesized outcomes.
Discussions

IPC is currently one of the most widely used VTE physical preventive devices in clinical practice. Although it has been continuously studied in recent years, clinical medical staff still have doubts about its effectiveness and safety\cite{28, 29}. Therefore, it is necessary to further update the evidence regarding the effectiveness and safety of IPC to guide the clinical practice. The results of this meta-analysis have showed that IPC is effective to reduce the risk of DVT, VTE and PE in patients undergoing surgery treatment.

Venous congestion, hypercoagulable state and vascular endothelial injury are recognized as the three major factors for the occurrence of VTE\cite{30}. Surgical patients need to be immobilized for a long time, surgical injury, the use of drugs such as anesthesia, muscle relaxation, and sedation during the operation, puts the patient in a high-risk state of thrombosis, plus intraoperative blood transfusion, hypothermia, laparoscopic pneumoperitoneum, lithotomy and lying position greatly increase the risk of VTE\cite{31, 32}. IPC is an effective method of thrombosis prevention, which can increase muscle contraction, promote lymphatic and venous blood circulation, and prevent partial accumulation of coagulation factors, thereby effectively preventing the occurrence of VTE. Both IPC and GCS are effective physical prevention methods for DVT\cite{33-35}. Graduated compression stockings(GCS) is designed according to the principle of sequential decompression\cite{36, 37}. The pressure at the ankle is the highest, and it gradually decreases upwards along the legs, squeezing the veins of the lower extremities, speeding up the blood return to the heart of the veins of the lower extremities, and reducing blood stasis to prevent the dilation of the venous lumen\cite{38, 39}. IPC mainly simulates the contraction and relaxation of lower extremity muscles through intermittent inflation and compression, and squeezes the veins of the lower extremities, thereby speeding up the
blood flow of the veins of the lower extremities, avoiding blood pooling in the veins of the lower extremities, promoting venous blood return to the heart, and protecting the function of the venous valve, to achieve the purpose of preventing the occurrence of DVT[40-42].

With the aging of the population, the number of people at high risk of clinical VTE has increased sharply[43]. Therefore, IPC is often used in combination with drugs in order to improve safety. With the widespread use of drugs in clinics, bleeding has become a major clinical concern. This meta-analysis was unable to analyze the bleeding risk of IPC due to the lack of included data. Compared with anticoagulants in previous studies[44, 45], IPC can reduce the incidence of bleeding events, but it is not yet possible to draw a certain conclusion on the incidence of major bleeding events and mortality[46]. This may be related to the insufficient number of studies and the different anticoagulants use in the researches. Compared with IPC alone, studies have shown that IPC combined with low molecular weight heparin (LMWH) can reduce the incidence of bleeding events. The IPC combined anticoagulant group and the anticoagulant group alone cannot draw a certain conclusion on the incidence of bleeding and major bleeding events[47]. It may be related to the heterogeneity between the studies and the insufficient number of studies. Therefore, the safety of use is subject to further analysis in follow-up research.

The results of previous studies[18, 48] are different from the results of this study, showing that intraoperative use of IPC will increase the incidence of postoperative DVT. The analysis may be due to the small sample size and the high risk of DVT in neurosurgery patients. Even if preventive measures are given, the risk of DVT is still very high. Ultrasound is generally performed when the patient has symptoms after surgery, but study[49] has shown that more than 50% of DVTs are invisible and asymptomatic. The literatures included in this study come from different populations,
and there is a certain degree of heterogeneity in the results, and most included studies did not assess the risk level of VTE during the operation before the preventive measures were given, and there may be insufficient prevention of high-risk patients. All these suggest that relevant specialized researches are needed in the future to further confirm the effect of intraoperative IPC in surgical patients. At the same time, it is necessary to explore or develop intraoperative VTE risk assessment tools to provide a more scientific basis for the prevention of intraoperative VTE.

Several limitations in this present meta-analysis should be considered. Firstly, the literature included in this study comes from different populations, and there is a certain degree of heterogeneity in the results, and most included studies did not assess the risk level of VTE during the operation before the preventive measures were given, and there may be insufficient prevention of high-risk patients. Secondly, we could not perform subgroup analysis based on the types of surgical procedures limited by collected data, relevant specialized researches are needed in the future to further confirm the effect of intraoperative IPC in surgical patients. Besides, it is necessary to explore or develop intraoperative VTE risk assessment tools to provide a more scientific basis for the prevention of intraoperative VTE.

Conclusions

In conclusion, the results of this meta-analysis have showed that intraoperative IPC can effectively reduce the incidence of postoperative VTE, and it is worthy of promotion and use in clinical surgery. In view of the relatively small number of RCTs at present and certain clinical heterogeneity in research population, interventions, outcome indicators in this meta-analysis, the effectiveness and safety of IPC in surgery still need to be confirmed by multi-center and large-sample clinical studies, to provide reliable evidence-based bases for the preventions and management of VTE in surgical
List of abbreviations

IPC: intermittent pneumatic compression
VTE: venous thrombosis
DVT: deep vein thrombosis
PE: pulmonary embolism
CNKI: China national knowledge infrastructure
RCTs: randomized controlled trials
NOS: Newcastle-Ottawa Scale
RR: risk ratios
CI: confidence intervals
MDs: mean differences
LMWH: low molecular weight heparin

Declarations

Ethics approval and consent to participate

In this study, all methods were performed in accordance with the relevant guidelines and regulations.

Our study did not need the Ethics approval and consent to participate since our study is a meta-analysis.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.
Competing interests

The authors declare that they have no competing interests.

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None.

Author contributions

Jianhua Li designed research; Yanping Yang, Jianhua Li conducted research; Yanping Yang, Jianhua Li analyzed data; Yanping Yang, Jianhua Li wrote the first draft of manuscript; Jianhua Li had primary responsibility for final content. All authors read and approved the final manuscript.

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Notes: TKA, total knee replacement; THA, total hip replacement; GBM, glioblastoma; HFS, hip fracture surgery; GCS, graduated compression stockings; MBVF, mean blood flow speed; PVBF, peak blood flow velocity; BFV, blood flow volume; PLT, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; D-D, D-dimer.
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Figure 1 PRISMA flow diagram
Figure 2 Forest plot for the incidence of DVT in the included RCTs
Figure 3 Forest plot for the incidence of VTE in the included RCTs
Figure 4 Forest plot for the incidence of DVT in the included retrospective cohort studies

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</table>

Total events: 30, 102

Heterogeneity: Chi² = 6.90, df = 5 (P = 0.23); I² = 28%

Test for overall effect: Z = 2.15 (P = 0.03)
Figure 5 Forest plot for the incidence of PE in the included retrospective cohort studies
Figure 6 Funnel plots for synthesized outcomes