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The use of intermittent pneumatic compression to prevent venous thromboembolism in neurosurgical patients—A systematic review and meta-analysis

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ABSTRACT

Objective: The incidence of venous thromboembolism (VTE) remains high despite the use of low-molecular weight heparin (LMWH) and compression stocking (CS). We aimed to evaluate the use of IPC as VTE prophylaxis in neurosurgical patients.

Patients and methods: We conducted meta-analysis to assess the use of IPC as VTE prophylaxis in neurosurgical patients from several databases.

Results: There was a total of 7.515 subjects from 5 studies. Reduction in VTE incidence was demonstrated by the IPC group (OR 0.40 [0.31, 0.52], $p < 0.001$; I^2: 44 %). IPC was shown to reduce the incidence of deep venous thrombosis (DVT) (OR 0.43 [0.32, 0.57], $p < 0.001$; I^2: 0 %) compared to the control group. Incidence of pulmonary embolism (PE) was lower (OR 0.42 [0.25, 0.70], $p < 0.001$; I^2: 80 %) in IPC. Upon sensitivity analysis, PE was significantly lower in IPC (OR 0.24 [0.13, 0.45], $p < 0.001$; I^2: 0 %). Subgroup analysis on patients undergoing neurosurgical intervention (operation) and receiving LMWH + CS shows a markedly reduced incidence of VTE (OR 0.37 [0.28, 0.50], $p < 0.001$; I^2: 3 %), DVT (OR 0.39 [0.28, 0.54], $p < 0.001$; I^2: 0 %), and PE (OR 0.22 [0.11, 0.43], $p < 0.001$; I^2: 0 %) in IPC.

Conclusion: Intermittent pneumatic compression was associated with less VTE in neurosurgical patients, especially in those who received neurosurgical interventions, however, the certainty of evidence remained inadequate for creating a strong recommendation and further randomized controlled trials are needed before drawing a definite conclusion.

1. Introduction

Venous thromboembolism (VTE) is a clinical entity comprising of deep venous thrombosis (DVT) and pulmonary embolism (PE), it is one of the major concern in the neurosurgical procedure. Reports in 2011 showed that DVT occurred in approximately 23 % of the neurosurgical patients despite combined mechanical and chemoprophylactic measures for VTE and PE in approximately 3.5 % [1,2]. Approximately 39 % of patients undergoing craniotomy developed DVT despite the combined use of low-molecular weight heparin (LMWH) and compression stocking (CS) in a 2013 report. Hence, an additional measure beyond LMWH and CS may be needed.

Intermittent pneumatic compression (IPC) simulates the movement of the lower extremity and may be of value [3]. Whether addition of IPC to the established VTE prophylaxis regiment translates to a clinical benefit in neurosurgical patients remain controversial. In the setting of

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intensive care, a paper reported that the use of IPC on top of VTE prophylaxis only adds up unnecessary cost [4]. On the other hand, a cost-analysis in orthopedic patients undergoing lower limb arthroplasty showed that the inclusion of IPC results in the most cost-effective VTE prophylaxis regiment [5]. The aim of this systematic review and meta-analysis is to evaluate the latest evidence on the use of IPC as VTE prophylaxis in neurosurgical patients. This systematic review was conducted and written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Material and methods

2.1. Search strategy

We performed a comprehensive search on topics that assesses the use of IPC in neurosurgical patients with keywords [“intermittent pneumatic compression” and “deep venous thrombosis”] and its synonym from inception up until November 2019 through PubMed, EuropePMC, Cochrane Central Database, ScienceDirect (research articles, peer-review filter), ProQuest, ClinicalTrials.gov, and hand-sampling from potential articles cited by other studies. The records were then systematically evaluated using inclusion and exclusion criteria. We also perform hand-sampling from references of the included studies. Two researchers (R.V and E.Y) independently performed an initial search, discrepancies were resolved by discussion. A PRISMA flowchart of the literature search strategy of studies was presented in Fig. 1.

2.2. Selection criteria

The inclusion criteria for this study are all studies that assess the use of IPC in neurosurgical patients. We include all related clinical researches/original articles and exclude animal studies, case reports, review articles, and non-English language articles.

2.3. Data extraction

Data extraction and quality assessment were done by two independent authors (R.P and H.D) using standardized extraction form which includes authors, year of publication, study design, inclusion criteria, intervention group, control group, VTE, DVT, PE, sample size, subject characteristics, and follow-up duration.

2.4. Statistical analysis

To perform the meta-analysis, we used RevMan version 5.3 software (Cochrane Collaboration) and STATA MP 16.0 (StataCorp LP). We used the odds ratio (OR) and a 95 % CI as a pooled measure for dichotomous data. Inconsistency index (I^2) test, which ranges from 0 to 100 %, was used to assess heterogeneity across studies. A value above 50 % or $p < 0.05$ indicates statistically significant heterogeneity. We used the Mantel-Haenzsel method for OR with a fixed-effect model for meta-analysis, and a random-effect model was used in case of heterogeneity. Small study effect was assessed using a regression-based test (Harbord test) for binary outcomes. Sensitivity analysis by removing one study at a time (leave-one-out) was done in an attempt to single out the cause of heterogeneity. Subgroup analysis was done for patients undergoing

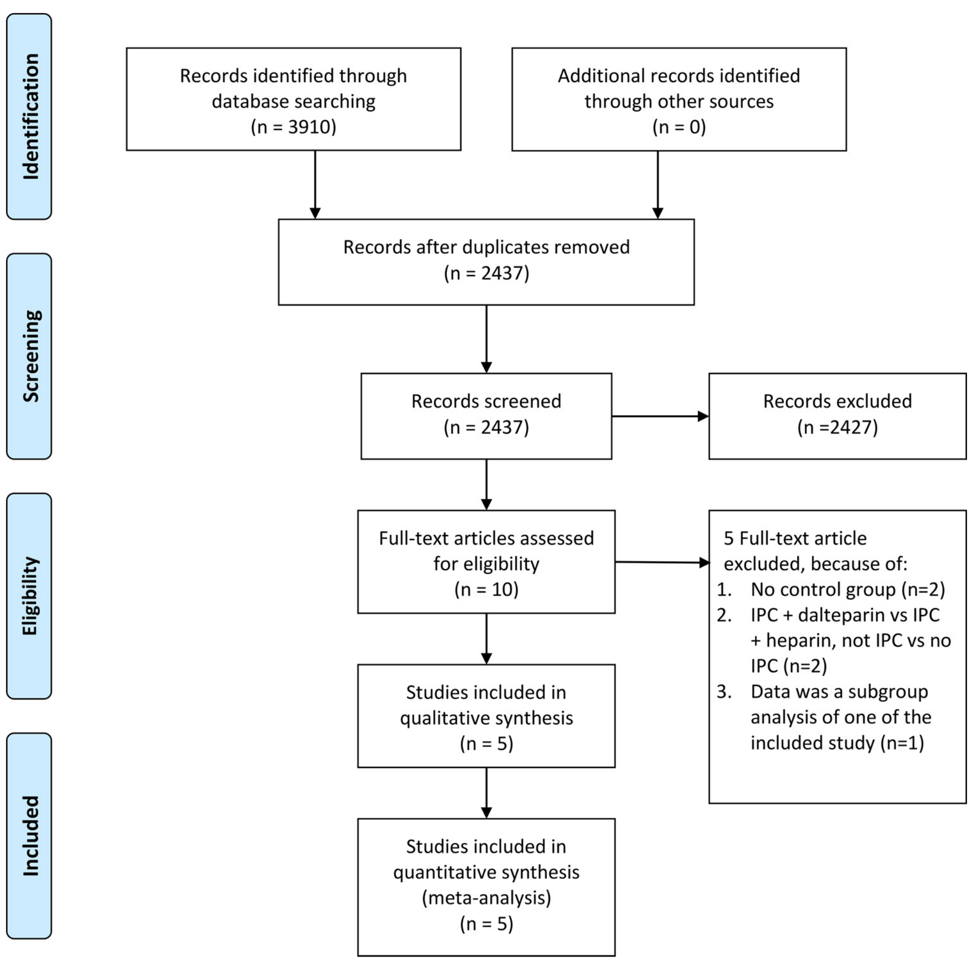

Fig. 1. Study flow diagram.

Table 1
Characteristics of Included Studies.

Author	Study Design	Patients	Intervention	Control	Assessable Sample Size (n)	Male (%)	Age (years)	Follow-up
Prell 2018	RCT	Elective craniotomy	Intraoperative IPC + CS + LMWH	CS + LMWH	94 (41/53)	41.5/47.2	54.2 ± 10.9/55.8 ± 15	6 days post-op
Chibbaro 2017	Cohort	Neurosurgical Intervention	Perioperative IPC + CS + LMWH (Post-operative IPC in high risk patients)	CS + LMWH	6987 (3169/3818)	52/49	60 ± 5/58 ± 6	Unclear
Frisius 2015	Cohort	Neurosurgical Patients using Intraoperative MRI	Intraoperative & Postoperative IPC	CS + LMWH	207 (86/121)	60.4	44.3 ± 3.8	Unclear
Kurtoglu 2004	RCT	Head/Spinal Trauma	IPC on admission to ICU + LMWH	LMWH	120 (60/60)	39.2	37.1 (18–76)	7 days post discharge
SCITI 2003	RCT	Spinal Trauma	IPC + UFH	LMWH	107 (49/58)	79.6/89.7	40.6 ± 17.3/38.5 ± 16.2	2 weeks

CS: Compression Stocking; **ICU:** Intensive Care Unit; **IPC:** Intermittent Pneumatic Compression; **LMWH:** Low-molecular Weight Heparin; **MRI:** Magnetic Resonance Imaging; **RCT:** Randomized Controlled Trial; **UFH:** Unfractionated Heparin.

neurosurgical intervention (operation) and patients receiving CS. All P values were two-tailed with a statistical significance set at 0.05 or below. The certainty of the evidence was assessed by using the Guideline Development Tool by GRADEpro GDT.

3. Results

There was a total of 3910 potential articles on the initial search, and 2437 records remained after removing the duplicates. 2427 articles were excluded after screening the titles and abstracts. 10 potentially relevant full-text articles were explored and a total of 5 studies were excluded because 1) no control group (n = 2), 2) IPC + dalteparin vs. IPC + heparin, not IPC vs. no IPC (n = 2), 3) data was a subgroup analysis of one of the included study (n = 1). We included 5 studies (3 randomized controlled trials [RCT] and 2 observational retrospective studies) for qualitative synthesis and meta-analysis (Fig. 1, Table 1). There was a total of 7.515 assessable subjects from 5 studies [6–10].

3.1. Characteristics of the included studies

Neurosurgical intervention was performed in all patients of 3 studies by Prell et al., Chibbaro et al., and Frisius et al. These patients also received CS and LMWH as prophylaxis in both IPC and control group. In these studies, IPC was performed only intraoperatively in 1 study, intraoperatively and postoperatively in 1 study, and perioperative with additional postoperative IPC in high-risk patients in 1 study. The other 2 studies were performed in patients with trauma, head/spinal trauma in 1 study, and spinal cord injury in another, in which not every patient included received neurosurgical interventions. Both IPC and control group in these studies did not receive CS.

3.2. Venous thromboembolism

Reduction in VTE incidence was demonstrated by the IPC group (OR 0.40 [0.31, 0.52], $p < 0.001$; I^2: 44 %, $p < 0.13$) [Fig. 2A].

3.3. Deep venous thrombosis subgroup

Intermittent pneumatic compression was shown to reduce the incidence of DVT (OR 0.43 [0.32, 0.57], $p < 0.001$; I^2: 0 %, p = 0.46) compared to the control group [Fig. 2B].

3.4. Pulmonary embolism subgroup

Incidence of PE was similar (OR 0.64 [0.13, 3.06], p = 0.58, I^2: 80 %, p = 0.002) in both groups in a random-effect model, but was lower (OR 0.42 [0.25, 0.70], $p < 0.001$; I^2: 80 %, p = 0.002) [Fig. 2C] in IPC upon a fixed-effect model analysis. Upon sensitivity analysis, we found that SCITI 2003 study was the cause of heterogeneity, and upon exclusion, PE was significantly lower in IPC (OR 0.24 [0.13, 0.45], $p < 0.001$; I^2: 0 %, p = 0.55).

3.5. Neurosurgical intervention subgroup

Subgroup analysis on patients undergoing neurosurgical intervention (operation) shows that IPC was associated with reduced incidence of VTE (OR 0.37 [0.28, 0.50], $p < 0.001$; I^2: 3 %, p = 0.36) [Fig. 3A], DVT (OR 0.39 [0.28, 0.54], $p < 0.001$; I^2: 0 %, p = 0.63) [Fig. 3B], and PE (OR 0.22 [0.11, 0.43], $p < 0.001$; I^2: 0 %, p = 0.49) [Fig. 3C].

Subgroup analysis on studies providing CS to all of the patients (comprising of same studies as neurological intervention subgroup) showed reduced VTE (OR 0.37 [0.28, 0.50], $p < 0.001$; I^2: 3 %, p = 0.36), DVT (OR 0.39 [0.28, 0.54], $p < 0.001$; I^2: 0 %, p = 0.63), and PE (OR 0.22 [0.11, 0.43], $p < 0.001$; I^2: 0 %, p = 0.49).

Subgroup analysis on studies that did not provide CS to all of the patients showed a non-significant reduction in VTE (p = 0.76), DVT

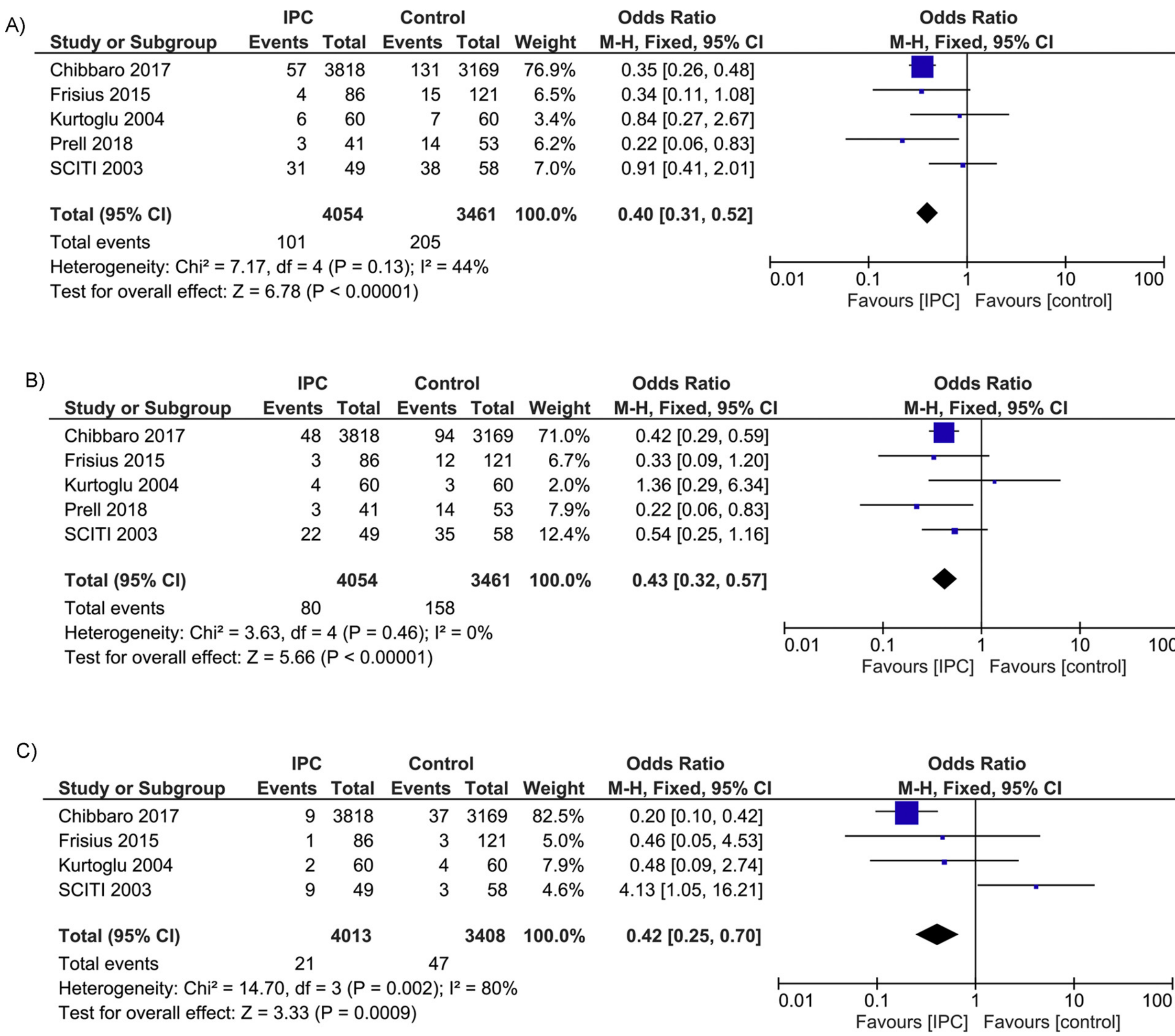

Fig. 2. Venous Thromboembolism. IPC reduce the incidence of VTE (2A). IPC was also shown to lower the risk for DVT (2B) and PE (2C). **DVT:** Deep Venous Thrombosis; **IPC:** Intermittent Pneumatic Compression; **PE:** Pulmonary Embolism; **VTE:** Venous Thromboembolism.

(p = 0.21), or PE incidence (p = 0.23); albeit limited interpretation due to small sample size.

3.6. Publication bias

Funnel plot analysis revealed a slight asymmetry in VTE and DVT, PE showed a more asymmetrical funnel-plot. Regression-based Harbord's test for small-study effects was not significant for VTE (p = 0.431), DVT (p = 0.586), and PE (p = 0.352).

3.7. GRADE assessment

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) were performed, showing that IPC has a low certainty of evidence for the prevention of VTE and DVT. There is a very low certainty of evidence for PE prevention which improved to low certainty upon subgroup analysis of patients that underwent neurosurgical intervention (Table 2).

4. Discussion

Intermittent pneumatic compression reduces the incidence of VTE (including DVT and PE subgroup) in neurosurgical patients, especially in those who received neurosurgical interventions.

Stasis, hypercoagulability, and endothelial injury are the components of triad described by Virchow [11]. There are several mechanisms involving blood vessel, muscle, and subcutaneous tissue that may explain the protective effect of IPC on VTE. The generated pressure causes a sudden accelerated forward motion, resulting in a pulsatile movement of venous blood, ensuing distention of the compliant lumen [3]. Increased blood flow velocity causes subsequent increase in shear stress along the endothelial cells lining of the lumen which facilitates the clearance of valve sinuses [3]. In the muscle, the pressure from IPC increase muscle contraction which decreases venous pressure, increase AV gradient, increase arterial blood flow, and reduce stasis [3]. In the subcutaneous tissue, there will be an increase of stretch or strain and an increase in the interstitial pressure, forcing interstitial fluid into the circulation thus reducing edema [3]. These aforementioned effects act on the "stasis" component of Virchow's Triad. In the blood vessel, the shear and stretch of the endothelial cells promote the synthesis of nitric oxide, increase in prostacyclin, inhibition of tissue factor pathway, a decrease of plasminogen activator inhibitor, and increase of tissue plasminogen activator thus prevent the formation of fibrin [3,12,13]. These effects alleviate the "hypercoagulability" part of Virchow's Triad.

Chibbaro et al. identify those at high-risk as patients with previous VTE, concomitant radiotherapy/chemotherapy, cardiac implants,

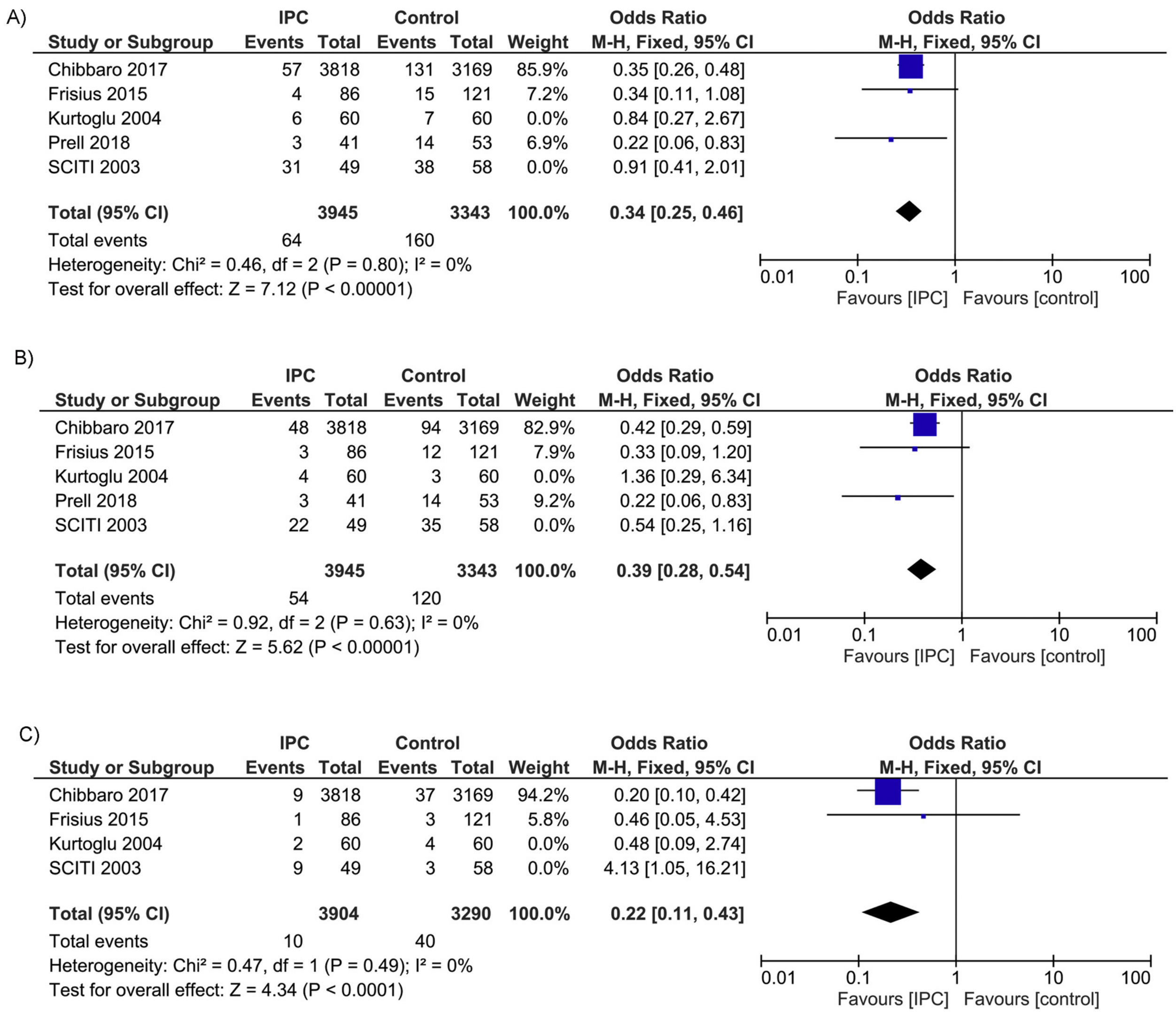

Fig. 3. Subgroup analysis in patients receiving neurosurgical interventions. IPC reduce the incidence of VTE (2A). IPC was also shown to lower the risk for DVT (2B) and PE (2C). **DVT:** Deep Venous Thrombosis; **IPC:** Intermittent Pneumatic Compression; **PE:** Pulmonary Embolism; **VTE:** Venous Thromboembolism.

patients undergoing resection for brain or spinal tumors, and surgery lasting > 4 h [6]. High-risk patients in IPC group was also given postoperative IPC in addition to perioperative IPC in their study. Frisius et al. also provides postoperative IPC to the patients, whether postoperative IPC is necessary is yet to be determined. Kurtoglu et al. and SCITI 2003 study did not show any benefit of adding IPC to prevent VTE. Their study did not include CS to both intervention and control groups. There is a possibility of a synergistic effect between IPC and CS in neurosurgical patients. Although studies did not demonstrate any augmentation of efficacy in patients receiving IPC and CS [14], there is no evidence for using IPC without CS in neurosurgical patients.

The patients were given IPC upon admission to intensitve care unit (ICU) in Kurtoglu et al. study, whether any of the patients underwent neurosurgical intervention was unclear. However, Kurtoglu et al. stated that they excluded patients that underwent craniotomy. In SCITI 2003, only 50 % of the patients underwent surgical procedures. Hence, these two studies do not enroll surgical patients exclusively, there is a possibility that IPC benefit is more pronounced in surgical patients. Duration of surgery is one of the known risk factors for VTE in neurosurgery [7,9], a complex intracranial surgery may take hours, increasing the duration of venous stasis, and predisposing patients to VTE. A recent study showed that IPC is not beneficial in critically ill patients in intensive care, which might indicate that IPC efficacy as VTE prophylaxis seemed to be limited to specific types of patients [15].

Furthermore, Kurtoglu et al. and SCITI 2003 include only patients with trauma, on the other hand, the three remaining studies included patients with intracranial tumors. Intracranial tumor is a known risk factor for VTE [16,17] and may have different pathophysiological basis than patients with trauma and immobilization, influencing the response to IPC.

The study by SCITI 2003 has a very high drop-out rate leaving only 22.5 % of the original sample. Furthermore, the amount of VTE in these patients reached above 60 % of the remaining patients, which is higher than the rest of the studies. This study was a significant cause of heterogeneity in the pooled data and had to be interpreted with caution. It was shown that the rate of DVT in patients with spinal cord injury (21.6 % was due to metastasis) receiving mechanical thromboprophylaxis, in which 86.5 % underwent surgery, was 43.2 % [18]. The rate of DVT was almost as prevalent as SCITI 2003 study.

A study by Macdonald et al. investigate the use of dalteparin + IPC vs. heparin + IPC in patients undergoing craniotomy, in this study, both drugs were found to be safe [19]. The rate of VTE in the aforementioned study was 2 % (both were DVT) [19] similar to the pooled DVT incidence in IPC group of this meta-analysis. Ting et al. reported a 4 % postoperative DVT in patients undergoing craniotomy and receiving CS + IPC [20]. Epstein et al. demonstrated 1 % VTE incidence among patients undergoing single-Level anterior corpectomy/fusion and 7 % VTE among patients undergoing multilevel anterior

Table 2
GRADE Assessment.

Certainty assessment							No of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPC	Control	Relative (95 % CI)	Absolute (95 % CI)	
VTE											
5	observational studies	serious[a]	not serious	not serious	not serious	strong association	101/4054 (2.5 %)	205/3461 (5.9 %)	**OR 0.40** (0.31 to 0.52)	**33 fewer per** 1000 (from 39 fewer to 26 fewer)	⨁⨁◯◯ LOW
DVT											
5	observational studies	serious[a]	not serious	not serious	not serious	strong association	80/4054 (2.0 %)	158/3461 (4.6 %)	**OR 0.43** (0.32 to 0.57)	**25 fewer per** 1000 (from 31 fewer to 19 fewer)	⨁⨁◯◯ LOW
PE											
4	observational studies	serious[a]	serious[c]	not serious	not serious	publication bias strongly suspected strong association[b]	21/4013 (0.5 %)	47/3408 (1.4 %)	**OR 0.42** (0.25 to 0.70)	**8 fewer per** 1000 (from 10 fewer to 4 fewer)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **DVT:** Deep Vein Thrombosis; **IPC:** Intermittent Pneumatic Compression; **OR:** Odds ratio; **PE:** Pulmonary Embolism; **VTE:** Venous Thromboembolism.
Explanations.
[a] Unclear Length of Follow-up in some studies.
[b] Asymmetrical Funnel Plot.
[c] High Heterogeneity.

corpectomy/fusion with posterior fusion [21]. In Ebeling et al. study, a glioblastoma multiforme subgroup of Frisius et al. study showed that 8 % developed DVT and 1.3 % developed PE, in their study, there was no significant difference between the incidence of VTE between IPC and control group [22]. Hence, from this observation, IPC may have a varying effect based on the type of surgical procedures. However, such differences may also be incidental and may be confounded by various factors. For example, patients with glioblastoma multiforme are expected to have a higher risk for coagulopathy and as reported by the authors, the sample size may be too small to detect meaningful differences or different pathophysiological mechanism of VTE in glioblastoma renders IPC unhelpful [22].

Despite widely used, the optimal method for pneumatic compression remains uncertain. A study compared sequential compression device with simultaneous, sequential compression in spine and knee operations showed that both graded sequential compression devices have similar efficacy [23]. A study showed that simultaneous compression with fixed cycling rate has superior hemodynamic efficacy compared to alternate compression with adjusted cycling rate in post total knee arthroplasty, however, whether it translates to clinical benefit remains unknown [24].

Major concerns related to IPC use are compliance, proper fit, and discomfort. When ambulating the device can be detached and reattached when the patient rests. A study on nonambulatory trauma patient reported that only 19 % of the patients (16.9 % of the observations) were compliant with the physician's order [25]. Spinal column injuries were associated with increased compliance. In a newer report, the frequent misapplications of IPC devices were reported in 49 % of the observations in ICU patients [26]. Such errors might limit the effectiveness of IPC's.

4.1. Limitations

There was a lack of RCTs evaluating the evidence in patients that received a neurosurgical intervention. The funnel plot for PE subgroup is asymmetrical which may indicate publication bias. The certainty of evidence remained low, and a subsequent are needed before drawing a definite conclusion regarding this matter.

5. Conclusion

Intermittent pneumatic compression was associated with a reduction in the incidence of VTE (including DVT and PE subgroup) in neurosurgical patients, especially in those who received neurosurgical interventions. However, the certainty of evidence remained inadequate for creating a strong recommendation, further RCTs are needed before drawing a definite conclusion.

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CRediT authorship contribution statement

Raymond Pranata: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Supervision. **Hadrian Deka:** Conceptualization, Data curation, Investigation, Writing - original draft. **Emir Yonas:** Data curation, Writing - original draft. **Rachel Vania:** Data curation, Investigation, Writing - original draft, Project administration. **Alexander Edo Tondas:** Investigation, Writing - review & editing. **Antonia Anna Lukito:** Investigation, Writing - review & editing. **Julius July:** Investigation, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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