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Original Research Article

The Efficacy of Intermittent Pneumatic Compression Device as an Alternative Measure to Pharmacological Prophylaxis for Venous Thromboembolism in Postoperative and Post-Trauma Patients: An Integrative Review

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Abstract: Thromboprophylaxis methods mainly include pharmacological and mechanical options, such as intermittent pneumatic compression devices (IPCDs). In a specific population (post-operative and post-traumatic patients) the risk of VTE is combined with increased risk of bleeding complication which is the side effect of the pharmacological prophylaxis. The aim of this integrative review is to assess the effectiveness and safety of IPCDs as an alternative choice to pharmacological prophylaxis in post-surgery and post-trauma patients. The electronic databases CINAHL, MEDLINE EMBASE, and Cochrane libraries were systematically searched for primary studies. We included studies that had evaluated the effectiveness and safety of the sole use of IPCD against the sole use of pharmacological prophylaxis in post-surgical and post-trauma patients. A total of 13 eligible articles were identified. Post-trauma patients were enrolled only in two studies and the remaining 11 studies were conducted on post-surgery patients. The findings suggest that IPCDs, compared with pharmacological prophylaxis, are equally effective in reducing DVT, PE and mortality rate and offered a reduced risk of bleeding. There were no consistent relations between the types of IPCDs and the clinical outcomes. This review demonstrates that there is lack of strong evidence informing the comparative effectiveness of IPCDs against pharmacological prophylaxis. Additionally, there is very limited evidence that can inform which type of IPCD is more appropriate as a thromboprophylaxis tool. Thus, until further robust research is conducted, it is difficult to conclude that IPCDs can replace pharmacological prophylaxis for post-surgery and post-trauma patients.

Keywords: Venous thromboembolism, Intermittent pneumatic compression device, Pharmacological prophylaxis, Surgery, Trauma

INTRODUCTION

Venous thromboembolism (VTE) which means the formation of blood clot in the vein, is one of the most common cause of death that can be prevented among the hospitalized population [1]. Clinically, VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The adverse consequences of DVT and PE are significant for both patients and health organizations. It affects around 900,000 Americans each year, causing a substantial level of morbidity and mortality. Currently, the average number of incidents caused in the US each year by VTE is between 48 to 122 per 100,000 [2]. This preventable issue also often results in an immense impact on the mortality and morbidity rate and resource utilization, and a prolonged hospital stay [3]. DVT and PE are estimated to result in 300,000 deaths per year and hundreds of thousands of hospitalizations [2]. Paffrath, Wafaisade [4] reported that the occurrence of PE in trauma patients was linked to a mortality rate of 25.7%. In addition to the significant increase in resource utilization (including hospital beds and medical interventions), the diagnosis and treatment costs for DVT or PE, per patient, have increased to approximately $10,804 and $16,644 respectively [3]. Thus VTE is a serious issue for both patients and healthcare facilities as it has a huge impact on morbidity, mortality, and healthcare costs.

VTE can be caused by a number of complicated risk factors [5]. Surgical intervention and

trauma are two of the main factors known to significantly increase the risk of developing VTE [6]. This is because one or more components of Virchow's triad (stasis, hypercoagulability and endothelial injury) are present in these patients [7]. Evidence has shown that the presence of one factor of Virchow's triad can increase the risk of VTE; however, the combination of more than one element of the triad greatly increases this risk [8].

In addition to the increased risk of VTE, this specific population, surgical and traumatic patients, are at increased risk of bleeding complication [6]. Currently there are various guidelines available to prevent VTE, however, there is no standard approach [9]. These preventative measures mainly include mechanical prophylaxis (graduated compression stockings (GCS) or intermittent pneumatic compression device (IPCD) and pharmacological prophylaxis [10]. One issue that further complicates the prevention of DVT in postoperative and trauma patients is the fact that these patients are at high risk of bleeding, which is further increased with the use of pharmacological thrombprophylaxis [6].

The implementation of either strategy (mechanical prophylaxis or pharmacological prophylaxis) as an optimal method for reducing the risk of the development of VTE remains controversial in this specific population [9]. Sadaghianloo and Dardik [9] also, claimed that guidelines directing best practice in such population are not clear. Hence, care providers often have to decide if pharmacological prophylaxis is appropriate. In making this decision, the clinician needs to balance between the risk of bleeding with the risk of developing VTE and consider whether IPCD alone is more appropriate.

IPCD has been utilized as an effective and safe tool for hospitalized patients in the prevention of DVT and PE [9]. It is hypothesized that IPCD has two different mechanisms in order to prevent the occurrence of VTE. The first is through increasing venous blood flow velocity and the other is by activating fibrinolysis [11-13]. This means that IPCD prevents VTE through two pathways of Virchow's triad: stasis and hypercoagulability. It is also suggested that IPCD works on the third pathway of Virchow's triad as it helps to activate endothelial cells and increase the release of nitric oxide [14]. Furthermore, IPCD has one important advantage over pharmacological prophylaxis in that it does not impair normal clotting thus does not result in bleeding complications [15]. This makes IPCD an attractive and potential alternative model of VTE prevention for patients who have an increased risk of bleeding.

Care providers face uncertainty when making decisions regarding the optimal and safe choice of VTE prophylaxis. The purpose of this review is to evaluate if IPCD can be considered an effective and safe alternative to pharmacological prophylaxis in terms of preventing the occurrence VTE and reducing the risk of bleeding in hospitalized post-operative surgical patients as well as those who have been admitted due to trauma. Moreover, there does not appear to be any current review to evaluate the studies that compare the effectiveness and safety of the sole use of IPCD against the sole use of pharmacological prophylaxis in post-surgical and post-trauma patients. Only one review did so but in different populations including surgical and non-surgical [16]. Therefore, this review aims to assess if IPCDs can replace the pharmacological agents as a safe and effective thromboprophylaxis means in a specific population (post-operative and post-traumatic patients) in whom there is increased risk of VTE and bleeding complication. This integrative review will explore available primary studies that investigating the effectiveness of these two intervention in isolation.

METHODS

An integrative literature review method has been selected for this study. This method provides strategies to enhance rigour in an integrative review by using the 5-stage integrative review process, which includes identifying the purpose, collecting data, evaluating the collected data, analyzing the data, and interpreting and presenting the results [17]. In order to address the aim of this review through conducting a systematic search, the following key questions have been developed:

Q1: Is using the IPCD associated with a decrease rate of VTE when compared with pharmacological prophylaxis?

Q2: Is using the IPCD associated with fewer bleeding complications when compared with pharmacological prophylaxis?

Q3: Does the effectiveness of the IPCD vary based on the characteristics of the used devices?

Search Strategies

The electronic databases CINAHL, MEDLINE and EMBASE were systematically searched for primary studies, which address the comparative effectiveness of IPCD against pharmacological agents in terms of preventing VTE. Cochrane Libraries were also searched in order to ensure that all relevant reviews and systematic reviews were found. MEDLINE, accessed via PubMed®, was searched based on the analysis of the medical subject headings (MeSH) terms and text words of key articles identified. The search was then narrowed down to peer-reviewed primary research studies conducted on adult humans and published in the English language. No specific publication date was required, because this review partially focuses on the IPCD type and whether the changes in its characters over time, affected its performance.

In addition to the initial search, a manual search was conducted in order to locate publications that may not have been identified. This was achieved by reviewing the reference lists of the included studies, related reviews, and conference abstract papers.

Inclusion and Exclusion Criteria

The search resulted in a large number of papers. However, two investigators applied pre-specified inclusion and exclusion criteria to narrow the search and identify the most appropriate articles that address the condition of interest.

Inclusion Criteria:

1. Studies providing data comparing the effect of IPCD against pharmacological thromboprophylaxis
2. Studies must report at least one of these outcomes: DVT, PE, bleeding complications, and mortality.
3. The studies must examine hospitalized post-operative and post-traumatic population.

Exclusion Criteria:

1. Studies that used IPCD as an additional thromboprophylaxis tool to another preventative measure.
2. Where data relating to comparisons of interest could not be effectively extracted from the reported findings.
3. IPCD intervention followed by pharmacological agent in the same group should be included in your exclusion criteria

Search Outcome

For the purpose of this review and in order to retrieve the most relevant articles, the PRISMA guidelines were incorporated to inform the search process of this review. This search yielded 13 articles that represent the only full-text articles that met the eligibility criteria of this review (Figure 1).

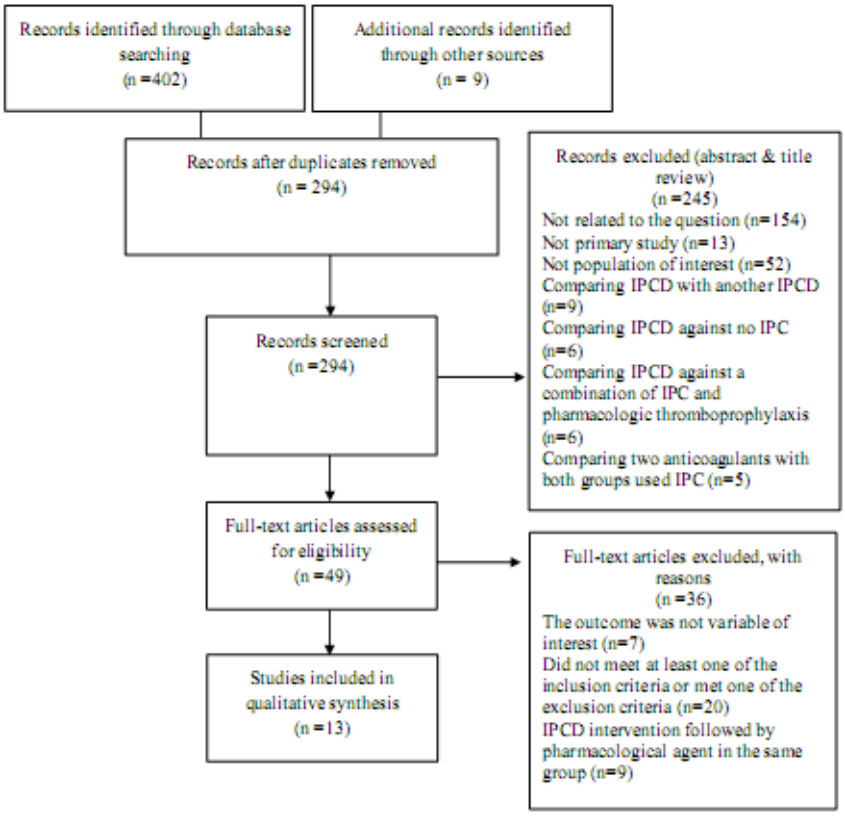

Fig-1: PRISMA flow diagram

Quality Assessment (Appraisal)

All studies retrieved were RCTs. As mentioned above, this is obviously due to the nature of the chosen topic and the clinical question used to address this topic. Thus, two assessors used the Critical Appraisal Skills Programme (CASP) to assess the risk of bias for each trial [18]. The risk of bias was assessed by evaluating each trial against the following domains: allocation concealment, blinding, intention to treat (ITT), participants' follow-up and outcome reporting.

FINDINGS

A total of 13 Randomized Control Trials (RCTs) were included in this review. All of the included studies compared IPCD with pharmacological prophylaxis. Although the search targeted all types of primary studies regardless of their methodology, the final studies were all RCTs. This is obviously due to the

nature of the topic, which focuses on the evaluation of the comparative effectiveness of IPCD and pharmacological prophylaxis in terms of preventing VTE. Among the thirteen identified studies, two only evaluated the comparative effectiveness of IPCD for patients who had been hospitalized due to trauma. The remaining 11 studies were conducted on post-operative patients who had undergone surgical intervention. All of the studies measured the primary outcome (DVT) and one of the secondary outcomes (PE, bleeding complications, and mortality). Thirteen studies assessed the risk of DVT (11 in post-surgery patients and 2 in post-trauma patients). Twelve studies assessed the risk of PE (ten in post-surgery patients and two on post-trauma patients). Six studies assessed the mortality (four in post- surgery patients and two in post-trauma patients). Finally, ten studies assessed the risk of bleeding (eight in post-surgery patients and two in post-trauma patients). It is noteworthy that different types of IPCDs with a clear variation in the characteristics were used in these studies. Table 2, provides an analytical summary of the studies included in the review.

In order to evaluate the comparative effectiveness and safety of IPCDs against pharmacological prophylaxis, it is imperative to assess each study's clinical outcomes, including DVT, PE, mortality, and the risk of bleeding. Additionally, for the purpose of this review, the identified studies were categorized in terms of post-operative and post-trauma patients. As explained earlier, this specific population (surgical and trauma patients) are, similarly, at increased risk of VTE and bleeding complications. However, it is important to consider the possible differences between these two populations (the process and the type of injuries, clinical presentation, and excessive fluid replacement in trauma patients differ from patients who have undergone an elective operation). Therefore, these discrepancies affect the coagulation process and the effectiveness of the prophylaxis method which is being used. Findings of identified articles, therefore, will be themed in accordance to the clinical outcomes (DVT, PE, mortality, and the risk of bleeding) and will be assessed separately in two subgroups (post-operative and post-trauma patients).

Deep Vein Thrombosis (DVT)

Comparative Effectiveness in Post-Surgery Patients

With regards to the DVT events, 11RCTs (Tables 2: studies 1-8, 11-13) evaluated the effectiveness of the IPCDs against pharmacological thromboprophylaxis in patients who underwent elective surgeries. Three trials [19-21] statistically showed that IPCDs significantly reduce DVT incidents compared with the use of pharmacological prophylaxis. One additional study [22] found that IPCDs were slightly more beneficial than pharmacological prophylaxis. Another five studies [23-27] showed that there is no difference between both methods in terms of the development of DVT. In contrast, two studies [28, 29] indicated that, despite the overall effectiveness of the two methods, pharmacological prophylaxis was observed to be slightly more beneficial than IPCDs.

In their RCT, Borow and Goldson [20] enrolled, in his RCT, five hundred patients from five surgical specialties were studied. Patients treated with IPCDs were associated with the lowest incidence of thrombosis in this study. Of 79 patients treated with IPCDs, nine developed DVT, with an incidence rate of 11.3% compared to 17.9%, 19.5%, and 26.7% for patients treated with aspirin, heparin, and dextran respectively. The p values were not reported. Similarly, Santori, Vitullo [21] found in their RCT that, in terms of patients who had undergone joint arthroplasty, there was a statistically significant difference between the effects of IPCDs and pharmacological prophylaxis in terms of the prevention of DVT. Thirty-five percent (n=65) of the subjects who were treated with pharmacological prophylaxis developed DVT, with 16 major DVT events and 7 minor events. However, only 13% (n=67) of the subjects who were treated with IPCDs developed DVT, with three major and six minor events ($p < 0.005$) [21]. McKenna, Galante [19] demonstrated similar findings, despite the low sample size: 46 participants. They reported that the rate of DVT events is reduced for patients who were treated with IPCDs compared to patients who were treated with pharmacological prophylaxis [19]. In addition, one study found that IPCDs are slightly more beneficial than pharmacological prophylaxis in terms of reducing the risk of DVT [22]. Pitto, Hamer [22] showed that the rate of DVT in the pharmacological group was double that of the IPCD group (six vs. three DVT incidents, respectively [p value < 0.05]).

In contrast, two studies indicated that, despite the overall effectiveness of the two methods, pharmacological prophylaxis was observed to be slightly more beneficial than IPCDs [28, 29]. Warwick, Harrison [28] reported that the occurrence of DVT in their IPCD group was 18% (n = 136) compared with 13% (n = 138) in the pharmacological prophylaxis group (p = 0.29); however, the authors noted that the DVT events in the IPCD group were related to a type of DVT known as isolated thrombus, which is not considered clinically important.

Table 2: The description of the studies included in the review

Author/ year	Allocation Concealment, Blinding, Intention to Treat (ITT), Lost to Follow-Up	Study design	Interventions and No. of Patients	Theme	Population type	Duration of the treatment	Outcome ratio IPCD vs. Drug		
							DVT	PE	Bleeding
1.McKenna *et al*, 1980 [19]	Adequate, no blinding, analysis not by ITT, 6.5% did not complete the study	RCT (one centre)	Thigh and calf pumps (n=10) or control (n=12) or aspirin 325 mg (n=9) or aspirin 1300 mg (n=12)	DVT, PE, bleeding complications, and mortality	Surgical; postoperative (TKR)	Until discharge from hospital	1 vs. 8 patients	1 vs. 1 patient	0 vs. 1 patients
2.Borow *et al*, 1981 [20]	Inadequate, no blinding, analysis by ITT, all complicated the study	RCT (multi-centres)	Calf pumps (n=79), heparin 5000 U twice daily (n=86), aspirin 600 mg twice daily (n=78), TEDS (n=91), or control (n=89)	DVT and PE	Surgical; postoperative (general surgical)		9 vs. 23 patients	1 vs. 4 patients	_
3. Santori *et al*, 1994 [21]	Adequate, no blinding, analysis by ITT, all completed the study	RCT (one centre)	Foot pumps (n=67) or heparin 5000 U 3 times daily (n=65)	DVT, PE, bleeding complications, and mortality	Surgical; postoperative (THR)	7–10 days	9 vs. 23 patients	0 vs. 1 patients	0 vs. 9 patients
4.Kosir *et al*, 1996 [23]	Unclear, single blinded, analysis not by ITT, 21% did not complete the	RCT (one centre)	Thigh and calf pumps (n=25) or control (n=45) or heparin 5000 U	DVT	Surgical; postoperative (general surgical procedure)	Pumps for 48 hours Heparin for 7 days	0 vs. 0 patient	0 vs. 0 patient	_

	study		twice daily (n=38)						
5.Stone *et al*, 1996 [24]	Unclear, no blinding, analysis by ITT, all completed the study	RCT (one centre)	Calf pumps (n=25) or LMWH (n=25)	DVT and PE	Surgical; postoperative (THR)	Until hospital discharge	1 vs. 1 patient	0 vs. 0 patient	3 vs. 7 patients
6.Warwick *et al*, 1998 [28]	Adequate, single blinded, not by ITT, 4.8% did not complete the study	RCT (one centre)	Foot pumps (n=136) or LMWH (n=138) TEDs applied to both arms	DVT and PE	Surgical; postoperative (THR)	For 8 days	24 vs. 18 patients	1 vs. 0 patient	_
7.Maxwell *et al*, 2001 [25]	Adequate, single blinded, analysis not by ITT, 7.5% did not complete the study	RCT (one centre)	Calf and foot pumps (n=106) or LMWH (n=105)	DVT, PE, and bleeding complications	Surgical; postoperative (abdominal or pelvic surgery for gynecologic malignancy)	For 5 days after surgery	1 vs. 2 patients	0 vs. 0 patient	0 vs. 3 patients
8.Warwick *et al*, 2002 [26]	Adequate, single blinded, ITT, all completed the study	RCT (one centre)	Foot pumps (n=99) or LMWH (n=89) TEDs applied to both arms	DVT, bleeding complications, and mortality	Surgical; postoperative (TKR)	Until hospital discharge	57 vs. 48 patients	_	0 vs. 4 patients
9.Ginzburg *et al*, 2003 [30]	Adequate, no blinding, analysis by ITT, 44 patients withdrew	RCT (one centre)	Calf pumps to both leg or 1 arm and 1 leg (n=224) or LMWH (n=218)	DVT, PE, bleeding complications, and mortality	Surgical; Trauma	Until ambulating or hospital discharge	6 vs. 1 patients	1 vs. 1 patient	4 vs. 9
10.Kurtoglu *et al*, 2004 [31]	Inadequate, no blinding,	RCT (one	Calf pumps (n=60) for 48 h	DVT, PE, bleeding	Surgical; Trauma in ICU	Until discharge	4 vs. 3 patients	2 vs. 4	1 vs. 2 patients

	analysis by ITT, all completed the study	centre)	or LMWH (n=60)	complications, and mortality	(head & spinal trauma)	from ICU			
11.Pitto *et al*, 2004 [22]	Adequate, single blinded, ITT, all completed the study	RCT (one centre)	Foot pumps (n=100) or LMWH (n=100)	DVT, PE, and bleeding complication	Surgical; postoperative (THR)	For 12 days	3 vs. 6 patients	0 vs. 0 patient	0 vs. 3 patients
12.Chin *et al*, 2009 [29]	Unclear, no blinding, analysis by ITT, all completed the study	RCT (one centre)	control (n=110) TEDS (n=110) calf pumps (n=110) after surgery LMWH (n=110)	DVT, PE, and bleeding complications	Surgical; postoperative (TKR)	5–7 days or until the diagnosis of VTE was made for all patients	9 vs. 6 patients	0 vs. 0 patient	4 vs. 9 patients
13.Hardwick *et al*, 2011 [27]	Adequate, no blinding, analysis not by ITT, 0.8% did not complete the study	RCT (multi-centres)	Calf pumps (n=198) or LMWH (n=194)	DVT, PE, and bleeding complication	Surgical; postoperative (THR)	For 10 days	8 vs. 8 patients	2 vs. 2 patients	0 vs. 11 patients

- DVT, deep vein thrombosis; IPCD, intermittent pneumatic compression device; LMWH, low-molecular-weight heparin; TKR, total knee replacement; THR, total hip replacement; ITT, intention to treat

In the most recently conducted RCT in this review, Hardwick, Pulido [27] compared the effectiveness of IPCDs against pharmacological prophylaxis. Hardwick, Pulido [27] reported that the two methods are effective tools in terms of reducing the incidents of DVT; however, there were no statistically significant differences between them. Similarly, Stone, Limb [24] and Warwick, Harrison [26] found that DVT incidents were almost similar with both treatment options (pharmacological prophylaxis and IPCDs), indicating that both interventions are equally effective in terms of the prevention of DVT. This is consistent with the findings of Kosir, Kozol [23] and Maxwell, Synan [25]. They found that both IPCDs and pharmacological prophylaxis are equally effective forms of thromboprophylaxis for post-operative patients.

Comparative Effectiveness in Post-Trauma Patients

Two studies reported on the effect of IPCDs and pharmacological prophylaxis in terms of DVT among post-trauma hospitalized patients [30, 31]. In their RCT study conducted on 442 post-traumatic patients, Ginzburg, Cohn [30] noted an overall low incidence of thromboembolism in patients who had either form of thromboprophylaxis. Six patients (2.7%) in the IPCD group developed DVT compared with only one patient (0.5%) in the pharmacological group (p value = 0.122). However, in terms of two of the six patients who developed DVT, the IPCD was applied to only one of their legs because of the trauma. This study did not detect any differences in terms of the efficacy of the two methods of prophylaxis. The authors suggested that both prophylaxis interventions appeared comparable. The high rate of patient withdrawal (44 participants) because of compliance issues may have affected the reliability of these findings. Kurtoglu, Yanar [31] demonstrated similar findings. In their study, DVT developed in four of the patients (6.66%) in the IPCD group and three patients (5%) in the pharmacological prophylaxis group. Kurtoglu, Yanar [31] claimed that their study did not find any significant differences between the two groups regarding the DVT incidents. He recommended that both IPCDs and pharmacological prophylaxis are equally effective in terms of VTE prophylaxis.

Pulmonary Embolism (PE)

Comparative Effectiveness in Post-Surgery Patients

With regards to PE events, 10 RCTs (Table 2: studies 1, 2, 4-8, and 12-14) evaluated the effectiveness of IPCDs against pharmacological prophylaxis in terms of patients who had undergone elective surgeries. Generally, no differences between IPCDs and pharmacological prophylaxis were found in terms of their ability to reduce the incidence of PE. Five studies did not detect any case of PE using either intervention [22-25, 29]. Although two of the five studies used small sample sizes [23, 24], the results of the five studies were consistent, which suggests that IPCDs give results which are comparable with pharmacological prophylaxis in terms of preventing PE.

Three studies found that IPCD and pharmacological prophylaxis resulted in a low rate of PE events and that there were no statistically significant differences between them [19, 20, 27]. This indicates that they are equally effective in terms of reducing the risk of PE. Despite the high rate of DVT events (9 in the IPCD group and 23 in the pharmacological prophylaxis group), Borow and Goldson [20] found that PE incidents were detected in only four of the 500 participants and all of these patients were in the control group which did not receive any intervention.

Although the differences are not statically significant, two studies found a very slight difference between the use of IPCDs and pharmacological prophylaxis in PE events for post-surgery patients [21, 28]. Santori, Vitullo [21] found that one fatal PE was detected among the patients treated with a pharmacological agent and not one patient in the IPCD group was diagnosed with PE. Contrarily, in the study conducted by Warwick, Harrison [28], one of the patients in the IPCD group had a non-fatal PE. Meanwhile, no PE was detected in the group treated with pharmacological prophylaxis.

Comparative Effectiveness in Post-Trauma Patients

Two studies reported on the incidents of PE in terms of the effectiveness of IPCDs and pharmacological prophylaxis in post-trauma hospitalized patients [30, 31]. Ginzburg, Cohn [30] found similar rates of PE among both the IPCD and pharmacological prophylaxis groups (one incidence of PE in each group). Meanwhile, Kurtoglu, Yanar [31] studied 120 post-trauma patients (chosen at random) and found that the proportion of PE events in the pharmacological group was twice that which occurred in the IPCD group (3.3% vs. 6.6%, respectively [p value < 0.05]).

Bleeding complications

Comparative Effectiveness in Post-Surgery Patients

In terms of bleeding complications, eight studies (Table 2: studies 1, 3, 5, 7, 8, and 11-13) evaluated the effectiveness of IPCDs compared to pharmacological prophylaxis. Generally, the results of these studies demonstrated that IPCDs offered an advantage over pharmacological prophylaxis in that they reduce the risk of bleeding [19, 21, 22, 24-27, 29]. Out of the eight studies, six showed that IPCDs are significantly better than pharmacological agents in terms of minimising the risk of bleeding associated with thromboprophylaxis measures [21, 22, 24, 26, 27, 29]. Santori, Vitullo [21] observed that 9 out of the 65 patients who were being treated with pharmacological prophylaxis (13.8%) experienced excessive bleeding or

wound hematomas. Meanwhile, no such bleeding occurred in the IPCD group. The authors stated that the advantage of using IPCDs is that "the risk of excessive bleeding is avoided" [21]. Similarly, although the rate of DVT increased in the IPCD group as opposed to pharmacological group in Warwick et al.,s stydy [26], they found that four haemorrhagic complications were detected in the pharmacological prophylaxis group and none in the IPCD group. These complications included two cases of hematomata (one case of hematemesis and one case of hepatic artery bleed).

Chin, Amin [29] concluded that the most significant risk associated with pharmacological prophylaxis is bleeding. He found that 9 out of 110 cases developed bleeding in the pharmacological prophylaxis group compared to 4 out of 110 cases in the IPCD group. This indicates that bleeding complications make a pharmacological agent a less desirable thromboprophylaxis method. Additionally, Stone, Limb [24] did not find any difference in terms of the amount of blood lost into drains between the two interventions; however, seven patients in the pharmacological prophylaxis group needed at least two units of blood whilst only three patients needed transfusions of two units in the IPCD group. The larger proportion of blood transfusions required in the pharmacological prophylaxis group may have occurred as a result of blood loss into the tissues and possible bleeding into other sites. McKenna, Galante [19] reported one bleeding event in their pharmacological prophylaxis group. This patient experienced active bleeding from a hiatal hernia and salicylate gastritis. They also measured the bleeding time and found that it was noticeably prolonged in the pharmacological prophylaxis group more so than in the IPCD group.

Pitto, Hamer [22] reported that the major advantage of the use of IPCDs as thromboprophylaxis is the lack of associated side effects, including bleeding. In their RCT, bleeding complications (minor wound bleeding and post-operative bruising, swelling, and oozing of the wound) were significantly reduced among patients in the IPCD group compared to the patients in the pharmacological group. This finding has been confirmed by another RCT conducted by Hardwick, Pulido [27]. They reported 11 major bleeding episodes (6%) in the pharmacological prophylaxis group while no single event of bleeding was reported in the IPCD group. Additionally, the total number of transfusions received were 59 (30%) in the IPCD group compared with 74 (38%) in the pharmacological prophylaxis group (p value = 0.088). A 82 units of blood in total were required by patients in the IPCD group compared with 122 in the pharmacological prophylaxis group. The authors concluded that using IPCD offered a safe option as it reduced the bleeding complications associated with pharmacological prophylaxis.

Two studies showed that bleeding complications were similar between the two groups [25, 28]. Warwick, Harrison [28] found no difference between the two methods with regards to blood transfusion, intra-operative blood loss, and blood loss index; however, post-operative drainage, oozing, bruising, and swelling in the IPCD group were less than such incidents in the pharmacological prophylaxis group. This was supported by Maxwell, Synan [25] as the occurrences of bleeding complications (blood transfusions, of injection site, or hematoma, and laboratory studies including platelet count, pro-thrombin time, haematocrit, and thromboplastin activated time) in the pharmacological prophylaxis group were not more than such occurrences in the IPCD group. Interestingly, for the three patients who developed intraoperative haemorrhage and the one patient with severe thrombocytopenia, pharmacological prophylaxis discontinued postoperatively. Thus, the bleeding complications associated with pharmacological prophylaxis may have occurred if this therapy was continued for these patients.

Comparative Effectiveness in Post-Trauma Patients

Two studies reported on the bleeding complications that arise from using IPCD and pharmacological prophylaxis in post-trauma hospitalized patients [30, 31]. Kurtoglu, Yanar [31] showed that one event (1.6%) of exacerbation of epidural hematoma occurred in each group (pharmacological prophylaxis and IPCD groups). The rates of haematuria, ecchymosis of injection site, and bleeding from tracheostomy site were 8.3%, 3.3%, and 1.6% in the pharmacological prophylaxis group and 6.6%, 0%, and 0% in the IPCD group respectively. Ginzburg, Cohn [30] found four minor bleeding events in the IPCD group compared with nine in the pharmacological prophylaxis group (p value = 0.245). They also reported that four patients developed major bleeding in each group. Although the total number of minor and major bleeding events in the pharmacological prophylaxis group was higher than in the IPCD group, the authors suggested that there is no significant difference between the two methods in terms of the bleeding complications that are associated with thromboprophylaxis (p value = 0.237).

Mortality

Only four studies reported on the outcome of mortality using IPCDs and pharmacological prophylaxis (Table 2: studies 3, 8, 9, and 10). Two of these studies were conducted on post-surgery patients (3 and 8) and two on post-trauma patients (9 and 10).

Comparative Effectiveness in Post-Surgery Patients

One study indicated that there was one death due to PE in the pharmacological prophylaxis group while no deaths were reported in the IPCD group [21]. In contrast to this, Warwick, Harrison [26] showed that

the rates of mortality were increased in the IPCD group compared with the pharmacological prophylaxis group. Of the patients who died in this study, one was in the pharmacological group and three were in the IPCD group. Despite this difference in the findings of these two studies, both concluded that the difference is not significant.

Comparative Effectiveness in Post-Trauma Patients

The results of the studies of Ginzburg, Cohn [30] and Kurtoglu, Yanar [31] are consistent as they both found that the mortality rate was similar using both methods. Ginzburg, Cohn [30] reported no deaths in either group. Similarly, Kurtoglu, Yanar [31] found that the mortality rate was seven (11.6%) and eight (13.3%) patients in the IPCD and pharmacological prophylaxis groups respectively. The p value of >0.05 indicates that there was no statistically significant difference between the two groups regarding the reduction of the mortality rate.

Characteristics of IPCDs

The information about IPCD characteristics that was reported in the included studies varies. Generally, IPCDs are characterized by the anatomical location of the sleeve, patterns of compression cycles, amount of pressure used, duration of inflation time and deflation time, and whether they are portable or non-portable devices.

All of the included studies reported on the anatomical locations of the IPCDs. The IPCDs were applied to the foot in four studies [21, 22, 26, 28] and the devices were applied to the patients' calves in seven studies [20, 24, 25, 27, 29-31]. In two studies, the devices were applied to the patients' calves and thighs [19, 23]. The compression cycles of the IPCDs were reported in seven studies with a different number of cycles per minute. In four studies [21, 22, 28, 30] the devices inflated three times per minute. In two studies [20, 29], the devices inflated once per minute. Only one study [19] used the frequency of two cycles per minute.

Seven studies reported on the amount of pressure applied during the inflation time of the IPCDs. The applied pressure varied widely among these studies. The pads of the IPCDs were inflated to achieve a high pressure of 130 mm Hg in three studies [22, 28, 30]. In contrast, in another three studies, the pads of the IPCDs were only inflated to achieve a pressure varying between 45-55 mm Hg [20, 27, 29]. Only one study used a pressure of 30 mm Hg for the participants [19]. The duration of the inflation time and deflation time was varied as the IPCDs' pads inflated and deflated in one second [22, 28, 30], over five seconds [19, 21], or over 15 seconds [20]. With regards to the type of inflation, only one study used the rapid inflation technique [21]. Only one trial reported that portable devices had been used [27]. The IPCDs were initiated either intra- or post-operative, but in none of the included studies were the devices applied pre-operatively. In four studies [19, 24, 25, 27] the IPCDs were initiated intra-operatively while the rest applied the devices post-operatively. The duration of the intervention widely varied (Table 2). Overall, it is obvious that there is inconsistency in the characteristics, options, and usage of IPCDs across the studies included in this review.

DISCUSSION

Prior studies have investigated the effectiveness of thromboprophylaxis measures. The majority thereof assessed the effectiveness and safety of the IPCDs in comparison to pharmacological prophylaxis. However, few of these studies evaluated the effectiveness and safety of the sole use of IPCD against the sole use of pharmacological prophylaxis in post-surgical and post-trauma patients. The only review identified in the literature that did compare the sole use of IPCD with pharmacological prophylaxis included surgical and non-surgical patients; thus, the findings cannot be applied directly to post-surgery and post-trauma patients who are at a greater risk of bleeding than the general hospitalized population [16]. Therefore, in order to assess if IPCDs can replace pharmacological agents as a safe and effective means of thromboprophylaxis for a specific population (post-surgery and post-trauma patients) in whom there is increased risk of VTE and bleeding complications, this integrative review has explored the available primary studies that have investigated the effectiveness of these two interventions in isolation.

The initial search strategy identified 294 studies; however, only 13 of those studies met the inclusion criteria for this review. This result can be explained by the fact that the topic of VTE prophylaxis has been widely studied with different standards of care; for example, studies compared one IPCD with another or compared IPCD with no IPCD. However; only a limited number of studies directly compared IPCD with pharmacological prophylaxis and met the inclusion and exclusion criteria. Of the 13 papers included in this review, only two examined the use of IPCD and pharmacological prophylaxis in post-trauma patients. The remainder focused on post-surgery patients. This review has investigated the existent literature and will now summarise the evidence on the role of IPCDs and pharmacological prophylaxis in terms of VTE prevention among post-surgery and post-trauma patients.

Although the findings were inconsistent, studies conducted on post-surgery patients showed that DVT rates seem to favour IPCD. In 4 out of 11 trials, the risk of DVT was reduced for patients treated with IPCD compared to those treated with pharmacological prophylaxis [19-22]. Another five trials showed almost

no difference in the DVT rates of the two interventions [23-25, 27, 29]. Only two studies indicated that, despite the overall effectiveness of the two methods, pharmacological prophylaxis was observed to be slightly more beneficial than IPCDs [26, 28]; however, in one of those studies [28], participant withdrawal was high. In the other study [26] the authors noted that DVT events in the IPCD group were related to a type of DVT known as isolated thrombi which is not considered clinically important. With regards to the PE incidents in post-surgery patients, the findings of this review indicated that the risk of PE among patients treated with IPCD did not appear to be statistically different from patients who were treated with pharmacological prophylaxis. Importantly, in five studies, not one PE event was reported [22-25, 29]. Most of the remaining five trials showed a low rate of PE in both groups. Only two studies reported on the mortality rate using the two methods [21, 26] with inconsistent findings. However, the authors of the two studies agreed that the mortality rates using the two prophylaxis methods were not significantly different.

These findings support the traditional understanding of VTE pathogenesis. According to the Virchow triad, venous stasis and hypercoagulability are two of three factors involved in the pathogenesis of VTE [32]. Studies have shown that IPCD can act as VTE prophylaxis in two ways: by activating fibrinolysis and increasing venous blood flow velocity [11-13]. Hence, it is perhaps not surprising that IPCD is effective in reducing VTE. Additionally, the low rates of DVT, PE, mortality, and bleeding complications in the majority of the individual studies that were associated with IPCD use, support the findings of the previous meta-analysis [16], which revealed that using IPCDs was more effective than not using prophylaxis at all in terms of reducing the incidents of DVT and/or PE.

Interestingly, bleeding complications (major and minor) were considerably lower when an IPCD was used compared with the use of pharmacological agents. Six out of the eight studies that reported on bleeding complications in post-surgery patients demonstrated that IPCD offered an advantage over the pharmacological prophylaxis in terms of reducing the risk of bleeding. Three thereof [21, 27, 29] provided highly significant results, thereby indicating that IPCD is a significantly better method than pharmacological agents in terms of minimizing the risk of bleeding associated with thromboprophylaxis measures. The most recent study in this review [27] reported 11 major bleeding episodes (6%) in the pharmacological prophylaxis group, while no single event was reported in the IPCD group. Two trials revealed that both interventions do not significantly differ in terms of bleeding [25, 28]. However, Warwick, Harrison [28] observed that post-operative drainage, oozing, bruising, and swelling were less frequent in the IPCD group. Additionally, Maxwell, Synan [25] found that, in three cases (not included in the final outcome), the use of pharmacological prophylaxis was discontinued due to intraoperative haemorrhage.

Only two studies conducted on post-trauma patients met the inclusion and exclusion criteria. Ibrahim, Ahmed [33] found evidence in their review that IPCDs reduce the incidents of DVT in post-trauma patients compared to not using prophylaxis at all. The present review supports this finding as it found an overall low rate of VTE (DVT and PE) for both IPCDs and pharmacological prophylaxis. With regards to the comparative effectiveness of IPCDs, Kurtoglu, Yanar [31] demonstrated that both IPCDs and pharmacological prophylaxis were equally effective in terms of reducing the risk of DVT. Although Ginzburg, Cohn [30] showed that there was an overall low rate of DVT events, the majority of these events were in the IPCD group compared to the pharmacological prophylaxis group (one vs six). In this study, however, a large number of patients withdrew from the study (44 out of 442 patients). This may have affected the study's results. Additionally, some of the patients who developed DVT in the IPCD group had the device applied on only one leg due to trauma issues. With regards to the rate of PE, IPCD was not superior to pharmacological prophylaxis in terms of reducing the rate of PE in post-trauma patients. Mortality rates were reported in only one study, which demonstrated a better outcome using IPCDs [31]. In addition, IPCDs were observed to be associated with less bleeding complications in post-trauma patients. Ginzburg, Cohn [30], Kurtoglu, Yanar [31] suggested using IPCD as a safe prophylaxis method for patients with an increased risk of bleeding.

This review found that no significant difference was demonstrated between post-surgery and post-trauma patients in terms of the major clinical outcomes. However, the limited number of trials included in this review conducted on post-trauma patients (two trials) may have limited the results related to post-trauma patients. Further work is needed in this area as there is a difference between how post-trauma patients and patients who have undergone elective surgery respond to prophylaxis. In post-trauma patients, the process of the injury, the severity of damage in blood vessels, and excessive fluid replacement may affect the coagulation pathways in different ways [8]. Thus, further studies which evaluate the effectiveness of the IPCDs in terms of reducing the risk of VTE among post-trauma patients are required.

Differences were observed in terms of the mechanisms of the ICPDs used in the identified studies. These differences included the anatomical location of the sleeve (foot, calf, and thigh), patterns of compression cycles, amount of pressure used, duration

of inflation and deflation, and conceptual differences (such as device portability). Malone, Cisek [12], recommended using high-pressure and rapid inflation in IPCD prophylaxis. Meanwhile, Morris, Giddings [34] found that decreased global fibrinolysis activity is associated with rapid inflation. Delis, Azizi [35] suggested a pressure of 120 to 140 mm Hg with a frequency of three or four compressions per minute. The evidence for these recommendations can be considered very poor [9]. This review, however, found that there was no definitive evidence or consistent associations between the specific characteristics of the IPCDs and their clinical outcomes. Moreover, there was also no clear pattern between the thromboembolic outcomes and the time of initiation of the IPCD (intra-operative and/or post-operative). Pierce, Cherian [36] provided a summary in their review which indicated that current IPCDs are not a homogeneous group and it is difficult to determine a specific type or characteristic as being more effective than another. This may give a rationale for the fact that IPCDs have recently been recommended by a number of published guidelines for the prevention DVT; however, apart from device portability, the types of IPCDs were not determined in these guidelines [9].

Due to the lack of sufficient evidence, other criteria may be applied in terms of deciding which types of IPCDs should be used. According to Pierce, Cherian [36], an individual and objective evaluation of an IPCD can provide criteria which can be used in selecting an appropriate IPCD. This includes patient comfort, safety, quality, performance (adjustable pressure and cycle), ease of setup, and battery-related features. Additionally, to ensure the compliance, the guideline recommended use of portable IPCDs with hour meters [9]. However, future studies should be performed to compare the new device models with pharmacological prophylaxis in terms of, safety, and effectiveness as well as the patients' adherence.

The limitations of this review are categorized according to those related to the methods of the review and those related to the included studies. This review differs from other published reviews. The inclusion eligibility limited the studies to those comparing IPCD with pharmacological prophylaxis without any combination in order to investigate the sole use of IPCD against the sole use of pharmacological prophylaxis. This resulted in the exclusion of trials which may have provided useful data. Another limitation is that this review aimed to investigate the comparative effectiveness of IPCDs against pharmacological prophylaxis only in post-surgery and post-trauma patients. As specified by our eligibility criteria, other patients (who are at risk of thromboembolic disease and bleeding simultaneously, such as hospitalized patients with liver disease) were not assessed in this review. Therefore, generalizing the results to other types of patients is not possible.

Regarding the limitations related to the included studies, the findings of this review highlighted important methodological limitations in the identified studies, including the lack of blindness of the investigators, inadequate concealment, and the relatively small sample sizes used in most of the studies. It was difficult for the trials which compared the use of IPCDs and pharmacological prophylaxis to "blind" the patients and treatment providers due to the nature of the intervention; however, investigators or treatment assessors can be blinded in terms of the treatment group of the patient. In the identified studies, only in five studies were the radiologists (assessors) blinded to the treatment group. Moreover, five of the included studies provided either inadequate or unclear concealment. This may rise the risk of biases in the assessment of the outcomes (DVT, PE and bleeding) and consequently may have influenced the results. A lack of high-quality trials with appropriate randomization and blinding may increase the risk of bias and it is difficult to provide solid evidence which can answer the key questions of this review. For this reason, future research is required. The second limitation is that the included studies used many different types of IPCDs. This heterogeneity was addressed by conducting further analyses in order to evaluate the relationship between the specific characteristics of the IPCD and its protective effect compared to pharmacological prophylaxis.

Based on the findings of this review, IPCDs, as a thromboprophylaxis method, are effective and safe in post-surgery and post-trauma patients. They help to reduce the risk of DVT and PE and the risk of bleeding complications. In this specific population, IPCDs, then, could be considered an important approach and could be recommended. Although this review demonstrates that IPCD alone afforded adequate prophylaxis against DVT and PE with less bleeding issues than pharmacological prophylaxis, this approach has limitations including a lack of standards for IPCDs. Additionally, some of the studies reviewed in this paper are also fraught with limitations, such as their limited methodological quality. This review, therefore, has identified areas in which the evidence is inadequate or inconclusive and further research is required. It is recommended that further studies which directly compare IPCDs with pharmacological prophylaxis are needed in order to determine the comparative effectiveness of the IPCD in post-surgery and post-trauma patients, especially in terms of post-trauma patients, where the currently available data is limited. Further studies are also needed in order to evaluate the practical use of IPCDs and to determine the optimal location, amount and duration of pressure, and

compression patterns required for IPCDs to prevent DVT and PE.

CONCLUSION

This review sought to identify if IPCDs can replace pharmacological agents as safe and effective thromboprophylaxis in post-surgery and post-trauma patients. The findings hereof indicate that IPCDs are comparable with pharmacological prophylaxis in terms of the major clinical outcomes of VTE and mortality events. IPCDs also offer a safer option than pharmacological prophylaxis for these patients as IPCD results in less bleeding complications than pharmacological prophylaxis. However, the existing data demonstrates a paucity of high-quality evidence and, thus, further research is required. Hence, it is difficult to answer the key question of this review: whether IPCDs can replace pharmacological prophylaxis. Therefore, until further robust research is conducted, it is recommended that health practitioners continue to use the current guidelines which recommend a combination of pharmacological prophylaxis with IPCDs during hospitalisation in order to prevent the occurrence of VTW and to leave the decision of using only IPCDs for care providers, in cases in which their patients are bleeding or at a high risk of bleeding, until the risk of bleeding is diminished.

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