Prevention of Venous Thromboembolism in Gynecologic Oncology Surgery

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Abstract

Gynecologic oncology patients are at a high-risk of postoperative venous thromboembolism and these events are a source of major morbidity and mortality. Given the availability of prophylaxis regimens, a structured comprehensive plan for prophylaxis is necessary to care for this population. There are many prophylaxis strategies and pharmacologic agents available to the practicing gynecologic oncologist. Current venous thromboembolism prophylaxis strategies include mechanical prophylaxis, preoperative pharmacologic prophylaxis, postoperative pharmacologic prophylaxis and extended duration pharmacologic prophylaxis that the patient continues at home after hospital discharge. In this review, we will summarize the available pharmacologic prophylaxis agents and discuss currently used prophylaxis strategies. When available, evidence from the gynecologic oncology patient population will be highlighted.

Venous Thromboembolism Incidence and Sequelae

Venous thromboembolism is a major cause of morbidity and mortality for patients with gynecologic cancers. Patients with malignancies and those undergoing pelvic surgery are known to be at higher risk of venous thromboembolism, making gynecologic oncology patients a particularly high-risk group. This increased risk for pelvic surgery patients is secondary to emboli that can arise from the lower extremities as well as the pelvic veins. When detected by a I 125-fibrinogen uptake scan, postoperative venous thromboembolism rates for patients undergoing gynecologic surgery in the absence of prophylaxis are as high as 15–40% [1]. A prospective study of 2,373 patients undergoing general, gynecologic, or urologic surgery for cancer reported a 2.1% 30-day incidence of clinically recognized

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venous thromboembolism [2]. There was a 2.0% incidence specifically among gynecologic oncology patients, 81% of whom received in hospital chemoprophylaxis and 30% of whom received extended duration prophylaxis at home. The overall death rate within 30-days of surgery was 1.72% with 46.3% of the deaths attributable to venous thromboembolism, making it the most common cause of postoperative death in this series. National statistics also suggest that pulmonary embolism is a common cause of preventable hospital death [3]. Venous thromboembolism has also emerged as a quality metric by which hospitals are compared to one another [4].

When patients with gynecologic cancers experience a venous thromboembolism, mortality is increased. For patients with ovarian cancer, the incidence of postoperative venous thromboembolism has been reported to be as high as 13.2%, even in the setting of prophylaxis, and postoperative VTE increases the mortality rate 2.3 times compared to patients who do not experience a venous thromboembolism [5]. Among endometrial cancer patients, venous thromboembolism also increases mortality. One study found that for endometrial cancer patients greater than 65 years of age, the incidence of venous thromboembolism within 6 months of diagnosis was 8.1%. For patients who experienced a venous thromboembolism within 6 months of diagnosis, mortality was increased 1.5 times compared to those without a venous thromboembolism [6]. It is important to note that this study included all stages of endometrial cancer, only patients greater than 65 and used a time period of 6 months which likely accounts for high observed cumulative incidence. Venous thromboembolism incidence also varies by histology for endometrial cancer patients. Patients with low grade (grade 1 or 2) histology have a venous thromboembolism incidence within 6 months of diagnosis of 3.6% compared to 6.1%–9.2% for grade 3 endometrioid and other high-risk histologies. Additionally, the type of malignancy is associated with risk of venous thromboembolism with ovarian cancer patients having the highest incidence among gynecologic cancers [7, 8]. Given the high incidence of venous thromboembolism among patients with gynecologic cancer and the availability of prophylaxis regimens to prevent venous thromboembolism, a structured and comprehensive plan for perioperative prophylaxis is necessary to care for these patients.

Risk Assessment

Virchow proposed a triad of risk factors contributing to venous thromboembolism: venous stasis, endothelial injury and hypercoagulable states. Many retrospective studies have given more specific risk factors such as increasing age, extent of surgery, length of surgical procedure, and many more. A prospective study specific to women undergoing gynecologic surgery found the following were independent risk factors (when evaluated by multivariable analysis): age, personal history of venous thromboembolism, cancer, African American race, prior pelvic radiation therapy, evidence of prior venous disease (varicose veins, ankle edema), blood loss and prolonged operating time. A risk assessment model was proposed, but has never been validated [9].

Currently, the American College of Chest Physicians (ACCP) recommends using risk assessment tools to assess postoperative venous thromboembolism risk among patients undergoing surgery [10]. According to these guidelines, patients are stratified preoperatively

into one of 4 risk categories: very low risk, low risk, moderate risk and high risk. These categories are based upon the relative venous thromboembolism incidence if no VTE prophylaxis is given. Specifically, very low risk patients have an incidence of less than 0.5%, low risk patients have an incidence of 1.5%, moderate risk patients have an incidence of 3.0%, and high-risk patients have a 6.0% incidence. The ACCP recommends that patients be categorized into these risk groups based on two different risk assessment tools, the Caprini score or the Rogers score (Table 1 and Table 2).

Both risk assessment tools provide a score based on patient and procedure risk factors that are associated with venous thromboembolism. These scores formalize the known relationships between various risk factors for venous thromboembolism that have been confirmed in large studies and assigned a relative weight to each in the form of points. Patients >60 years-old, those with cancer, those undergoing greater than 2 hours of anesthesia, those with bed-rest of greater than 4 days, higher Charlson co-morbidity scores, longer hospital stays and a personal history of venous thromboembolism are all factors that are known to increase venous thromboembolism risk.[10] Patients who experience postoperative complications, such as blood transfusions, pneumonia, and urinary tract infections, are also more likely to experience a postoperative venous thromboembolism than those who do not [11].

The Caprini score is a risk assessment score that was developed by Joseph Caprini in the early 1990s (Table 1) [12]. It assigns points to various venous thromboembolism risk factors and each patient is categorized by their resulting score as being at low, moderate, high or very high risk of venous thromboembolism. The score has the benefit of being easy to use and it has been used in practice by many surgical specialties, including validation studies in both general surgery patients and plastic and reconstructive surgery patients [13–15]. The Caprini score has also been studied in gynecologic oncology patients. A retrospective study calculated the Caprini score for 1,123 patients undergoing laparotomy with a gynecologic oncologist over a 7-year period and used the score as a predictor of venous thromboembolism. They found that 92% of patients scored in the highest risk category with a score of 5 or greater [16]. They observed a venous thromboembolism incidence of 3.3%. All in this study patients received mechanical prophylaxis and 40% received pharmacologic prophylaxis. All patients who experienced a venous thromboembolism were categorized in the highest risk group, meaning that in this population, the Caprini score was a highly specific tool for ruling out venous thromboembolism (100% of the patients with a score of less than 5 did not experience a thromboembolism). However, the Caprini score was not a very sensitive tool as only 37 of the 1033 patients with a score of 5 or greater experienced a venous thromboembolism (sensitivity 3.6%). A series of 17,713 patients, all with gynecologic cancers, reported from a national quality database, confirmed this with 97% of patients scoring in the highest risk group with a Caprini score of 5 or greater [7]. When the highest risk group was sub-stratified by score, the Caprini score was useful in discriminating relative venous thromboembolism incidence among gynecologic oncology patients. Patients with a score of 8 or higher had 2.1 times the odds of developing a venous thromboembolism within 30 days of surgery as those with a score of 5. An additional single institution prospective quality improvement study of 527 patients found that 96% of their patients with gynecologic cancers had a Caprini score in the highest group confirming the results of these

two studies [17]. Although the American College of Chest Physicians recommends the Caprini score as a tool to risk stratify patients undergoing gynecologic oncology surgery, these data highlight challenges to its use in this population.

The other risk score that the ACCP recommends for risk stratification is the Rogers score (Table 2). The Rogers score was developed in a population of general surgery patients using logistic regression modeling [18]. Points are assigned to various patient and procedure risk factors. Patients are categorized into risk groups on the basis of their final scores. Low risk patients are those with a score of less than 7, moderate risk are 7–10 and high risk are greater than 10. The Rogers score is not as extensively used as the Caprini score and has not been validated in additional populations beyond from the original development cohort. A single study has examined the use of the Rogers score among gynecologic oncology patients [7]. It found that among all gynecologic oncology patients, 0.2% of patients were categorized as low risk, 36.9% were moderate risk and 63.0% were high risk. The Rogers score was highly correlated with venous thromboembolism in that cohort; low risk patients had a 0% venous thromboembolism incidence; moderate risk patients a 1.0% incidence, and high risk patients a 2.2% incidence.

Risk assessment tools may be useful and are recommended because they allow clinicians to identify those patients at higher risk of developing a venous thromboembolism and use prophylaxis to prevent venous thromboembolism in those populations. Additionally, risk assessment tools also help to identify those patients at a lower risk of developing a venous thromboembolism. Identifying patients at lower risk allows clinicians to avoid prophylactic interventions that are costly and have risks, such as increased bleeding, for those patients who are less likely to benefit. A targeted prophylaxis regimen that is tailored to patient- and procedure-specific risk factors allows clinicians to maximize the benefits of prophylaxis and minimize the harms.

Prophylaxis Strategies

Modern day venous thromboembolism prophylaxis is not one-size fits all. There are many interventions and strategies that can be employed to decrease the risk of postoperative venous thromboembolism. These include mechanical prophylaxis, preoperative pharmacologic prophylaxis, postoperative pharmacologic prophylaxis and finally, extended duration pharmacologic prophylaxis that the patient continues at home after hospital discharge. Furthermore, within these categories, there are different drugs that can be used as pharmacologic prophylaxis as well as different forms of mechanical prophylaxis. It is important to note that may studies examining perioperative venous thromboembolism have used the end point of deep vein thrombosis or venous thromboembolism (deep vein thrombosis and pulmonary embolism), but have not been sufficiently powered to show a benefit in decreasing mortality. In this section, we will summarize the evidence for these strategies and when available, we will highlight evidence in gynecologic oncology patients.

Mechanical Prophylaxis

Mechanical prophylaxis methods act predominantly to decrease the venous stasis that contributes to an increased risk of postoperative venous thromboembolism. Venous stasis in the lower extremities decreases the mean blood flow and pulsatile index within the capacitance veins of the calf. This stasis results in an increased risk of a deep vein thrombosis. Mechanical prophylaxis methods decrease venous stasis and can be divided into two categories: passive methods and active methods. Passive methods include graduated compression stockings, while active methods include devices such as intermittent pneumatic compression devices that actively compress and release resulting in pulsatile flow out of the lower extremity. Both prevent venous stasis by increasing the blood flow velocity within deep veins and increasing venous return. Furthermore, preventing dilation of the capacitance veins is thought to prevent sub-endothelial tears in the vein wall, which would cause the release and activation of clotting factors. Active methods, such as intermittent pneumatic compression devices may also stimulate endogenous fibrinolysis by activating the production of tissue-type plasminogen activator by the venous endothelium.

Many postoperative thrombi occur either during surgery or in the immediate 24 hours after surgery and they most commonly occur in the capacitance veins of the calf. Use of passive mechanical prophylaxis methods, such graduated compression stockings, prevents pooling of blood in the calves which decreases venous stasis. These stockings exert graded compression with the degree of compression, and thus exerted pressure, decreasing from distal to proximal. Use of graduated compression stockings alone resulted in a 50% reduction in postoperative deep vein thrombosis formation, however, this efficacy can be improved significantly when they are combined with an additional prophylactic method [19]. Patients must be measured for appropriate stocking fit as improperly fitted stockings may act as a tourniquet resulting in a paradoxical increase in venous stasis [20]. Knee-length stockings are as effective as thigh-length stockings and are easier to apply making it less likely that they will roll down and create a tourniquet effect. Thus, many recommend that knee-length stockings be used preferentially [21]. Graduated compression stockings are low cost and are easy to use, however, passive mechanical prophylaxis methods such as compression stockings alone are insufficient prophylaxis when compared to active mechanical prophylaxis methods.

The most commonly used active mechanical prophylaxis method is the intermittent pneumatic compression device. These devices reduce stasis by compressing the calf at regular intervals with a sleeve that is inflated to approximately 50 mmHg by a pneumatic pump. When used intraoperatively and postoperatively after major gynecologic surgery, some studies have found these devices to be as effective as prophylactic pharmacologic prophylaxis in reducing deep vein thrombosis incidence [22–24]. In a study of postoperative gynecologic oncology patients, use intraoperatively and for 5 days postoperatively, was associated with a threefold reduction in venous thromboembolism compared to only perioperative compression [25]. However, to be effective, these devices should be used at least until ambulation and preferably throughout the hospital stay when the patient is immobile [10]. Real world challenges to this include the availability of the equipment and patient adherence. A study of obstetrics and gynecology patients noted that only 58% of

patients were using the pneumatic compression devices as indicated, highlighting the difficulty of using pneumatic compression devices alone in the real world setting [26].

Pharmacologic Prophylaxis Agents

In addition to mechanical prophylaxis, pharmacologic prophylaxis methods can be used to decrease the risk of postoperative venous thromboembolism. These medications act at different points in the clotting cascade to prevent thrombosis formation. Many new medications for pharmacologic prophylaxis have been introduced in recent years. As opposed to mechanical prophylaxis, some pharmacologic prophylaxis methods increase the bleeding risk and thus decisions about prophylaxis and choice of agent for a given patient must weigh the potential benefits of prophylaxis against the potential risks.

Unfractionated Heparin

Unfractionated heparin at a prophylactic dose is the most extensively studied method of thromboprophylaxis. Heparin prevents venous thromboembolism by binding and accelerating the action of anti-thrombin, a naturally occurring thrombin inhibitor. When given subcutaneously 2 hours prior to surgery and continued every 8–12 hours postoperatively, many trials have shown prophylactic dose unfractionated heparin (5000 units given subcutaneously) to be effective in decreasing the incidence of venous thromboembolism [10]. Two large meta-analyses of randomized trials of general surgery patients showed a two-thirds reduction in fatal pulmonary embolism with the use of prophylactic dose unfractionated heparin given every 8 hours compared with placebo or no prophylaxis [27, 28].

Prophylactic unfractionated heparin has also been used to decrease the incidence of venous thromboembolism among patients undergoing major gynecologic surgery for benign indications and was found to be effective at a postoperative dose of 5,000 units every 12 hours [10, 29]. However, this dosing schedule was found to be ineffective in high-risk patients with gynecologic cancer [30]. For patients with gynecologic cancers, the increased dosing schedule of 5,000 units of heparin 2 hours preoperatively and then given every 8 hours postoperatively has been shown to decrease the incidence of deep vein thrombosis detected by fibrinogen uptake scans and clinical evaluation [31].

Advantages of using unfractionated heparin include a long history of use, demonstrated efficacy in gynecologic oncology patients, and low cost. Disadvantages include the required frequency of administration with patients receiving 3 subcutaneous injections daily, concerns about perioperative bleeding, and finally the possibility of the patient developing heparin-induced thrombocytopenia. Although intraoperative blood loss has not been shown to be increased by the preoperative use of low-dose unfractionated heparin administration, an increase in postoperative bleeding has been noted, specifically an increase in wound hematoma formation [27]. Additionally, use for more than 4 days in a postoperative patient warrants monitoring of platelet counts every 2–3 days given the risk of heparin-induced thrombocytopenia (HIT). The incidence of HIT among all patients receiving prophylactic doses of heparin is approximately 0.1%, however, the incidence is higher in postoperative

patients and may be as high as 1–5% for patients receiving prophylaxis for 10–14 days [32–34].

Low Molecular Weight Heparin

Low molecular weight heparin has the same mechanism of action unfractionated heparin. Advantages of low molecular weight heparin over unfractionated heparin for venous thromboembolism prophylaxis include once daily dosing and a decreased risk of HIT. These benefits result from the molecular properties of low molecular weight heparin which result in a longer half-life, more predictable pharmacokinetics, and a greater bioavailability at lower serum drug levels. Low molecular weight heparins have also been shown to have at least equivalent efficacy in decreasing venous thromboembolism incidence when compared with unfractionated heparin [35, 36]. Furthermore, low molecular weight heparin has more anti-factor Xa and less anti-thrombin activity than unfractionated heparin. This has the potential to lead to decreased medical bleeding and postoperative wound hematoma formation. The risk of heparin-induced thrombocytopenia is less for patients receiving low molecular weight heparin compared to unfractionated heparin, and thus, platelet screening is not recommended [32].

Disadvantages of low molecular weight heparin relative to unfractionated heparin include increased cost and contraindication to use in patients with renal impairment [37]. Low molecular weight heparin is cleared renally and so the dose may need to be reduced or another agent selected in patients with renal impairment. Additionally, the benefits of the relatively long half-life of low molecular weight heparin in daily dosing can become a harm if it needs to be reversed as there is currently no reversal agent. Protamine sulfate can be used, but it is not as effective at reversing low molecular weight heparin compared with unfractionated heparin.

Since low molecular weight heparin was first studied in 1985 [38], multiple trials have shown it to be a reliable prophylactic method to decrease venous thromboembolism in postoperative patients. For gynecologic oncology patients, equivalent risk reductions were seen with the use of preoperative and daily postoperative low molecular weight heparin when compared with intermittent pneumatic compression devices [23]. A major prospective trial of 2,373 patients demonstrated a 2% incidence of clinical venous thromboembolism in patients undergoing general, urologic, and gynecologic surgery for cancer who received low molecular weight heparin prophylaxis [2]. Finally, a retrospective analysis of more than 3,500 patients found a significant reduction in both deep vein thrombosis and pulmonary embolism in patients receiving low molecular weight heparin prophylaxis compared with those patients who did not [39].

Direct Thrombin and Factor Xa Inhibitors

Fondaparinux is a specific indirect inhibitor of activated factor Xa which acts through its potentiation of anti-thrombin to decrease thrombus formation. Similar to low molecular weight heparins, caution must be exercised in patients with renal impairment, although a reduced dose has been shown to be safe in patients with a creatinine clearance of 20–50mL/min [40]. Fondaparinux has been studied as venous thromboembolism prophylaxis in

both orthopedic and general surgery patients, but has not yet been studied in gynecologic oncology patients [41, 42]. In a prospective randomized trial, fondaparinux was compared to a low molecular weight heparin, dalteparin, among patients undergoing major abdominal surgery. Equivalent efficacy between the two regimens was demonstrated in preventing postoperative venous thromboembolism [42]. In a sub-analysis of only the patients with cancer, fondaparinux was associated with a significant decrease in the incidence of venous thromboembolism. However, an increased risk of postoperative bleeding was found with fondaparinux when it was compared with low molecular weight heparin in orthopedic patients [41]. This increased risk of bleeding was not demonstrated in the trial of abdominal surgery patients. Therefore, fondaparinux may be appropriate for certain gynecologic oncology patients at the highest risk of venous thromboembolism in whom the risk of thrombosis is weighed against the risk of increased bleeding complications.

Direct thrombin inhibitors include drugs such as argatroban and dabigatran. Inhibition of thrombin prevents the conversion of fibrinogen to fibrin, an essential step in thrombus formation. Dabigatran was studied and is approved for prophylactic use in orthopedic patients undergoing hip and knee replacements. It was found to be non-inferior to low molecular weight heparin in terms of reduction in venous thromboembolism and postoperative mortality [43, 44]. Direct thrombin inhibitors have not been studied to date in gynecologic oncology patients.

Pharmacologic Prophylaxis Strategies

Dual Prophylaxis

Dual prophylaxis refers to using the combination of both mechanical and pharmacologic prophylaxis simultaneously. It is important to note that dual prophylaxis includes both a strategy in which mechanical prophylaxis is combined with pharmacologic prophylaxis given only after surgery or a strategy of mechanical prophylaxis combined with both preoperative and postoperative pharmacologic prophylaxis. Dual prophylaxis is recommended by the American College of Chest Physicians for patients at a high risk of developing a postoperative venous thromboembolism [10].

A Cochrane review found that dual prophylaxis is superior to both pharmacologic prophylaxis alone or mechanical prophylaxis alone in decreasing both deep vein thrombosis and pulmonary embolism in high-risk patients [45]. While randomized trials have been performed in orthopedics, urology, general surgery and neurosurgery, there are no trials specific to gynecologic oncology patients. However, a study examining venous thromboembolism before and after the introduction of a dual prophylaxis strategy in gynecologic oncology patients found a decreased odds of venous thromboembolism (OR 0.33, 95% CI 0.12–0.88) among those receiving dual prophylaxis when compared to the historical cohort who all received mechanical prophylaxis without uniform use of pharmacologic prophylaxis [46]. Furthermore, a decision analysis in high-risk gynecologic oncology patients found that a dual prophylaxis strategy combining intermittent pneumatic compression devices and low molecular weight heparin is cost-effective [47].

Another retrospective study in gynecologic oncology patients undergoing laparotomy found that 68% of patients who experienced a postoperative venous thromboembolism only received mechanical prophylaxis [16]. The baseline rate of dual prophylaxis in this series was 40% suggesting an over representation of mechanical prophylaxis alone among those patients diagnosed with a venous thromboembolism. A dual prophylaxis strategy has biologic plausibility for reducing both hypercoagulability and venous stasis in high-risk patients undergoing surgery. Although data from randomized trials in gynecology oncology patients are lacking, a dual prophylaxis strategy seems appropriate for this high-risk population [10].

Timing of Pharmacologic Prophylaxis

There are two issues with regard to the optimal timing of perioperative thromboprophylaxis. The first is whether preoperative pharmacologic prophylaxis is needed in addition to postoperative pharmacologic prophylaxis. The second is whether there is an optimal amount of time to wait postoperatively before giving the first dose of postoperative pharmacologic prophylaxis. Waiting too long could allow for thrombosis formation and initiating therapy too quickly could increase bleeding risk and resulting complications.

Studies evaluating the natural history of postoperative venous thromboembolism have shown that nearly 50% of venous thromboembolism events will begin within 24 hours postoperatively and an additional 25% will begin within 24–72 hours [1, 48]. Because venous thromboembolism can begin intraoperatively, most clinical trials evaluating either mechanical or pharmacologic prophylaxis have initiated the prophylactic method before surgery. Mechanical prophylaxis poses no bleeding risk and thus both graduated compression stockings and pneumatic compression devices should be placed before initiation of surgery and continued through the hospital stay. However, for pharmacologic prophylaxis it is plausible that preoperative administration could increase intraoperative bleeding risk. A meta-analysis including nearly 5,000 general surgery patients did show an increased risk of intraoperative and postoperative bleeding when low molecular weight heparin was used preoperatively compared to mechanical prophylaxis alone [36]. However, the majority of complications were minor wound hematomas, and there was no increase in serious bleeding events. Specific to the gynecologic oncology literature, a retrospective study of 122 patients undergoing gynecologic oncology surgery found no significant difference in blood transfusion or blood loss greater than 500cc among patients who received perioperative enoxaparin compared to those receiving mechanical compression alone [49].

Recent quality improvement projects have also shed light on this important topic. Investigators at Memorial Sloan Kettering Cancer Center examined the addition of preoperative pharmacologic prophylaxis along with the existing institutional practice of using postoperative pharmacologic prophylaxis and mechanical prophylaxis among patients undergoing major cancer surgery [50]. This population of 2,058 patients included approximately 15% gynecologic oncology patients. They found that the addition of preoperative pharmacologic prophylaxis to existing institutional practice significantly decreased the incidence of both deep vein thrombosis (1.3% to 0.2%) and pulmonary

embolism (1.0% to 0.4%) without any increase in either blood transfusions or major bleeding events. A smaller similarly designed quality improvement project of 527 gynecologic oncology patients compared a pre-intervention protocol of mechanical prophylaxis and postoperative pharmacologic prophylaxis to a post-intervention protocol that added both preoperative pharmacologic prophylaxis for all patients and extended duration prophylaxis for patients with cancer [17]. They observed a decrease in 90-day venous thromboembolism incidence from 6.7% to 2.3% and similarly found no increase in major postoperative bleeding events or infectious complications. Taken together, these data suggest that the administration of preoperative pharmacologic prophylaxis is likely safe and likely to benefit gynecologic oncology patients by decreasing venous thromboembolism incidence without increasing harms.

For surgeons who chose not to administer pharmacologic prophylaxis preoperatively, is there an optimal time to initiate postoperative low molecular weight heparin? This matter is currently unresolved as there is no data in the gynecology literature regarding postoperative timing. An analysis of many studies in orthopedic surgery patients describes a window of optimal low molecular weight heparin initiation from 6 hours to 12 hours postoperatively. Initiation of low molecular weight heparin at less than 6 hours postoperatively was associated with increased bleeding complications while delaying the first dose to more than 12 hours postoperatively results in an increased incidence of venous thromboembolism [51]. Until literature specific to the gynecologic oncology patient emerges, for the surgeon who does not want to give a preoperative dose of low molecular weight heparin, it seems prudent to administer postoperative doses of low molecular weight heparin between 6–12 hours after surgery to maximize the protective effect.

Extended Duration Prophylaxis

Among cancer patients who develop a venous thromboembolism postoperatively, 40% will do so more than 21 days after surgery. Among endometrial cancer patients diagnosed with venous thromboembolism, a recent study of a large national quality database found that 73% of minimally invasive surgery and 43% of open surgery patients are diagnosed with a venous thromboembolism *after* hospital discharge and the remaining 27% and 57% are diagnosed prior to hospital discharge [52]. The mean time to venous thromboembolism was 10 days for minimally invasive surgery patients and 14 days for open surgery patients. Clearly, these patients continue to have increased risk following the acute surgical event and hospital stay. Postoperative extended duration pharmacologic prophylaxis administered at home is a strategy to reduce these thromboembolism events. The original trial to examine this concept was a placebo-controlled trial of 332 high-risk cancer patients undergoing open abdominal surgery for cancer that compared low molecular weight heparin administered for 1 week postoperatively to 4 weeks postoperatively. When patient outcomes were evaluated at 28 days and 3 months postoperatively, the investigators found a 60% reduction in venous thromboembolism for the group that received 4 weeks of treatment compared to the 1 week group with no increase in bleeding [53]. Given these results, the American College of Chest Physicians recommends the use of extended duration prophylaxis for patients with cancer undergoing abdomino-pelvic surgery. However, a large claims-based study of privately insured patients found a low real world use of extended duration prophylaxis. In 2013,

extended duration prophylaxis was only prescribed to 18.3% of patients with ovarian cancer and 12.2% of patients with endometrial cancer [54]. Some of this may be due to extended duration prophylaxis not being given to patients undergoing minimally invasive surgery, however, even when this is factored in, the use of extended duration prophylaxis in this study was low. Increasing the percentage of patients receiving extended duration prophylaxis could be a target to decrease venous thromboembolism rates in gynecologic oncology.

Extended duration prophylaxis has also been studied in gynecologic oncology patients in at least two quality improvement projects. One, which we have already discussed, examined the addition of both pre-operative pharmacologic prophylaxis and extended duration prophylaxis of 14 days to the institution's current practice and found decreased incidence of 90-day venous thromboembolism [17]. The other examined a change in protocol that included only the addition of a 28-day postoperative course of low molecular weight heparin [55]. This study found a decrease in the 30-day venous thromboembolism incidence (2.7% to 0.6%) but failed to find a decrease in the 90-day incidence (3.7% versus 3.0%).

Special Populations

Minimally Invasive Surgery Patients

Minimally invasive surgery is increasingly being performed for gynecologic oncology patients making appropriate venous thromboembolism prophylaxis for this population an important consideration. Current guidelines and risk assessment scores do not differentiate between the risk of venous thromboembolism in minimally invasive surgery versus open surgery. Many have noted that minimally invasive surgery among gynecologic oncology patients is associated with a lower risk of postoperative venous thromboembolism, ranging from 0.4–2.2% [56–60]. Furthermore, comparison studies between patients undergoing minimally invasive gynecologic surgery and open gynecologic surgery, including patients undergoing surgery for endometrial cancer, have found that open surgery is associated with an increased odds of postoperative venous thromboembolism even when the differing prevalence of risk factors between the two groups are adjusted for [52, 61].

However, nearly all of these studies included patients that received some form of perioperative prophylaxis, making it difficult to conclude that no prophylaxis is necessary. The exception is a single study of 419 patients undergoing minimally invasive surgery for gynecologic malignancies, 84% of whom received no prophylaxis [56]. The rate of venous thromboembolism was 0.6% in patients who received no prophylaxis. Given the low incidence of venous thromboembolism after gynecologic oncology minimally invasive surgery, patients undergoing this form of surgery likely require less prophylaxis than those undergoing the same procedures via laparotomy. However, data are currently insufficient to specify what that regimen should be. A strategy of intermittent pneumatic compression prophylaxis is not associated with risks and should probably be used for all patients. Pharmacologic prophylaxis and extended duration prophylaxis could also be indicated for some minimally invasive surgery patients that have a high prevalence of patient specific risk factors. Risk assessment strategies could be useful to direct which minimally invasive surgery patients are likely to benefit from prophylaxis beyond mechanical prophylaxis alone.

Obese patients

The obese patient is at a higher risk of postoperative venous thromboembolism than the patient of normal weight. It is intuitive and biologically plausible that these patients would benefit from higher doses of unfractionated heparin or low molecular weight heparin. However, the optimal dose among obese gynecologic oncology patients has not yet been studied. Among bariatric surgery patients, twice daily administration of 40mg of enoxaparin was found to be superior to 30mg twice daily in reducing venous thromboembolism incidence.[62] Among morbidly obese (BMI   40 and weight > 100 kg) both medical and surgical hospitalized patients, twice daily dosing of 40mg of enoxaparin has also been shown to decrease VTE incidence by half compared to once daily dosing of 40mg [63]. In regards to unfractionated heparin, a higher dose is also needed for morbidly obese patients. Among the same cohort of morbidly obese hospitalized patients, 7500 units three time a day was superior to 5000 units in decreasing venous thromboembolism incidence [63]. Any of the above regimens would be reasonable for use among morbidly obese gynecologic oncology patients (BMI   40).

Inferior Vena Cava Filters

Placement of an inferior vena cava filter is indicated for patients who have an acute deep vein thrombosis or pulmonary embolism with an absolute contraindication to anticoagulation, such as a hemorrhagic stroke, recent or planned major surgery with persistent bleeding risk, or active bleeding [64]. Additionally, IVC filters may be considered for patients who already have a pulmonary embolism and are hemodynamically unstable, in whom an additional embolic event would be fatal. Preoperative prophylactic filter placement in patients at high risk of both thrombosis and bleeding, but without a current thrombosis is not recommended given the lack of a proven benefit. Studies suggest that IVC filters are currently over-utilized in the United States [65, 66].

Patients who have an IVC filter placed are at risk of complications and so the benefits must outweigh the risks in terms of placement. Specifically, the risk of venous thromboembolism is increased in patients who have an IVC filter placed [67, 68]. Additional risks include immediate complications such as bleeding and infection, however, the overall risk of immediate major complications is low at 0.3%. Later complications include IVC thrombosis that can occur in 3–30% of patients as well as filter migration and perforation of the filter through the wall of the IVC. For these reasons, the Food and Drug Administration recommends that low profile temporary removable filters be placed and removed within 25–54 days [69].

Conclusions

Venous thromboembolism is a major source of morbidity and mortality for gynecologic oncology patients. A dual prophylaxis strategy is the preferred strategy for the majority of gynecologic oncology patients undergoing laparotomy. Additionally, preoperative administration of pharmacologic prophylaxis is likely beneficial without significant harms for this population. For patients with gynecologic cancer undergoing a minimally invasive surgery, less prophylaxis is likely required given the decreased risk of venous

thromboembolism in these patients relative to their open surgery counterparts. However, data is limited to guide the extent of prophylaxis at this time. Mechanical prophylaxis using intermittent pneumatic compression is likely to benefit patients without the potential for harm and therefore, we believe it should be considered for use among all cancer patients undergoing minimally invasive surgery. Revised risk assessment tools and individual risk assessment could be useful in guiding the degree of pharmacologic prophylaxis given to gynecologic oncology patients undergoing minimally invasive surgery. Additionally, recommendations regarding prophylaxis dosing for patients with gynecologic malignancies can be made. Patients undergoing prophylaxis with unfractionated heparin should receive the medication at an interval no longer than every 8 hours. For patients with a BMI of greater than 40, dosing of low molecular weight heparin likely needs to be increased to achieve adequate prophylaxis. Lastly, IVC filters should be used sparingly and removed as quickly as is safe to decrease thrombosis and delayed complication risk.

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Highlights

Venous thromboembolism is a major source of postoperative morbidity and mortality.

Dual prophylaxis is recommended for gynecologic oncology laparotomy patients.

Minimally invasive surgery requires less prophylaxis than open surgery.

Table 1

Caprini Score

1 Point
Age 41–60 years
Minor surgery
BMI>25kg/m^2
Swollen Legs
Varicose veins
Pregnancy or postpartum state
History of unexplained or recurrent abortions (>3)
Oral contraceptive use or hormone replacement
Sepsis (<1 month)
Serious lung disease, including pneumonia (<1 month)
Abnormal pulmonary function
Acute myocardial infarction
Congestive heart failure
History of inflammatory bowel disease
Medical patient at bed rest
2 Points
Age 61–74 years
Major open surgery (>45 min)
Laparoscopic surgery (>45 min)
Malignancy
Confined to bed (>72 hours)
Immobilizing cast
Central venous Access
3 Points
Age >74 years
History of VTE
Family history of VTE
Congenital or acquired thrombophilias (ie Factor V Leiden, anticardiolipin antibodies, elevated serum homocystine, Prothrombin 20210A)
Heparin-induced thrombocytopenia
5 Points
Stroke <1 month
Elective arthoplasty
Hip, pelvis or leg fracture
Acute spinal cord injury (<1 month)

Above model adapted from the Caprini risk assessment model published in the American College of Chest Physicians Guidelines.[10]

Table 2

Rogers Score

1 Point
Wound class (clean/contaminated)
Preoperative hematocrit 38%
Preoperative bilirubin >1.0mg/dL
Dyspnea
Albumin 3.5 mg/dL
Emergency surgery
Female gender
ASA score of 2
2 Points
Disseminated cancer
Chemotherapy for malignancy within 30 days of the operation
Preoperative serum sodium >145mmol/L
Transfusion >4 units packed red blood cells in 72 hours prior to surgery
Ventilator-dependent
ASA score of 3, 4, or 5
Total procedure work relative value units 10–17
3 points
Work relative value units > 17
Integument surgery
4 Points
Intra-abdominal surgery

Above model adapted from Rogers et al.[18]