

## Venous Thromboembolism and Robotic Surgery: Need for Prophylaxis and Review of Literature

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### Abstract

Deep venous thrombosis (DVT) continues to be one of the devastating perioperative complications of any surgery. Pulmonary embolism (PE) is a catastrophic consequence of DVT which is better prevented than treated. Despite the laying down of various treatment protocols and improvements in prophylaxis, both DVT and PE continue to cause significant patient morbidity and mortality. Robotic surgery is a new feather in the revolutionary cap of minimal access surgery. Almost every part of the body can be operated by robot-assisted surgery for improved patient outcomes. It has several advantages in the form of lesser postoperative pain, early return to activity, lesser blood loss with consequent lesser transfusion requirements and better cosmesis. There have been very few studies on the incidence and management of DVT or PE following robotic surgeries. This review article aims to elucidate the above in robot-assisted abdomino-pelvic surgeries, especially in cancer patients.

**Keywords:** Venous thromboembolism; da Vinci robot; Cancer; Thromboprophylaxis; Deep vein thrombosis; Pulmonary embolism; Robot-assisted abdomino-pelvic surgery

### Abbreviations:

VTE: Venous Thromboembolism; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; LMWH: Low Molecular Weight Heparin; LDUH: Low Dose Unfractionated Heparin; ACCP: American College of Chest Physicians; AUA: American Urological Association; RARP: Robot-Assisted Radical Prostatectomy; SCD: sequential compression device; NICE: National Institute for Care and Excellence; ASRA: American society of regional anesthesia; TAP: Transverse Abdominis Plane; AHA: American Heart Association.

### Introduction

Thromboprophylaxis against thromboembolic events is of top-most priority among patient safety practices, as deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most common preventable causes of hospital deaths [1]. By definition, venous thromboembolism (VTE) is a disease that includes both DVT and PE. VTE results from an amalgamation of various hereditary or acquired risk factors, vessel wall damage, venous stasis and increased activation of clotting factors. DVT can involve the vessels of the lower extremity, upper extremity, mesenteric and pelvic veins. The prime aims of management of DVT consist of prevention of PE, post-thrombotic syndrome and recurrent thrombosis. There have been several articles on the importance of prophylaxis and management of postoperative DVT and PE. The protocols for their prevention and treatment are being laid down and regularly updated by the American College of Chest Physicians (ACCP) and AHA/ACC (American Heart Association) as well as by NICE (National Institute for Health and Care Excellence) guidelines [2]. Ever since the advent of minimally-invasive surgeries, there has been an unending, ongoing debate on the mode and duration of thromboprophylaxis required for such surgeries. This has been

compounded by the advancement in surgical technology and the rapid flourishing of robotic surgeries. There have been recent reports on the decreased incidence of DVT and/or PE following robot-assisted surgeries [3]. Currently, the da Vinci™ system of the Intuitive Surgical (Sunnyvale, USA) is the only FDA approved commercially available robotic system. There is an urgent need to review the existing recommendations for the prophylaxis and management of venous thromboembolism in the light of robotic surgery.

A thorough MEDLINE search was done for this review article with the key words: Robotic surgery; Minimally-invasive radical cancer surgery; Deep vein thrombosis; Pulmonary embolism; and Thromboprophylaxis. All the relevant articles related to venous thromboembolism in robot-assisted surgeries found in Google, Pubmed, ePUB and EBSCO (Elton B. Stephens Co., Massachusetts, USA) were fully reviewed.

### Background

#### Risk factors for venous thromboembolism and methods of thromboprophylaxis

Venous thromboembolism (VTE) is a preventable postoperative complication with potentially devastating consequences. There are several risk factors [4] for its occurrence. The major factors include polytrauma, malignancy, cancer therapy, hormone replacement therapy, obesity, immobility, smoking, advanced age, co-existing cardio-respiratory or renal failure, major surgery and inherited or acquired thrombophilia. Despite the widespread use of thromboprophylaxis, there has been a recent trend towards delayed occurrence of VTE, especially after discharge from hospital [5]. Detection of DVT may be difficult in the perioperative period and a high degree of suspicion must be maintained in high-risk patient population. Delay in the recognition and treatment of DVT can lead to several early and late complications [6] including pulmonary embolism (PE), venous gangrene, post-phlebotic syndrome and chronic

venous insufficiency. Even though venography is the most sensitive and specific study for DVT, compression ultrasonography is the most appropriate imaging study in the postoperative period. The Well's score is widely used to calculate pretest probability for DVT and clinical assessment of PE [7]. Two important criteria of special significance to this review are immobilization or surgery in the previous 4 weeks (1.5 points) and patients with malignancy on treatment, either treated in the last 6 months or palliative (1 point). In robotic surgeries, the postoperative return to normal activity is faster, which may account for the decreased incidence of VTE. In a recent Italian study done among urologic patients, the incidence of VTE was lower for endoscopic procedures [8]. Since the incidence of VTE is low for TURP (transurethral resection of prostate) and incontinence procedures, there is recommendation against specific prophylaxis other than early mobilization in these surgeries. The incidence is higher for radical prostatectomy, cystectomy and nephrectomy. Malignancy [9] poses an inherent risk for VTE due to associated procoagulant state and chemotherapy-induced thrombosis. Certain cancers, like that of the pancreas, ovary, uterus, brain, kidney or blood and advanced stage at presentation specifically increase the risk of VTE [10]. Chemotherapy itself is an independent risk factor for VTE. Certain chemotherapeutic agents, like platinum analogues [11] (Cisplatin, Carboplatin), anthracyclines, fluropyrimidines and Gemcitabine are specifically associated with increased risk of venous thrombosis. Detailed evaluation of the cycles of chemotherapy undertaken by the patient before robotic surgery for cancer is mandatory during the pre-anesthetic check-up. This also highlights that if robotic surgery is done for malignancy, then there is still a risk of VTE, which needs to be thoroughly evaluated by large multi-centre randomized controlled trials.

There are several methods [12] available for thromboprophylaxis which are routinely used in the perioperative setting for prevention of VTE and its attendant complications. The mechanical devices act by reduction of venous stasis in the lower extremities and release of antithrombotic factors from leg muscles. They mainly include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices and venous foot pumps (VFP). Pharmacologic thromboprophylaxis is achieved with low dose unfractionated heparin (LDUH), oral warfarin and subcutaneous low molecular weight heparin (LMWH). Newer anticoagulants [13] for VTE prophylaxis which act on Factor Xa or thrombin include Fondaparinux, Rivaroxaban, Apixaban, Dabigatran and Edoxaban. As per current ACCP recommendations [14], routine pharmacologic prophylaxis with LDUH (2 to 3 times a day) is given for major open urologic surgeries. In patients with severe renal dysfunction or established renal failure [15], intravenous unfractionated heparin may be given instead of LMWH. According to the ACCP recommendations, extended VTE prophylaxis with LMWH should be given for 4 weeks in patients undergoing major abdominal or pelvic surgery with concurrent risk factors like age more than 60 years, presence of cancer or past history of VTE. The incidence of VTE was found to be lower in patients undergoing laproscopic surgeries. There is an urgent need to revise the recommendations for routine thromboprophylaxis following robotic surgeries.

In the authors' opinion, the following table highlights the type thromboprophylaxis which may be considered for various types of abdomino-pelvic robotic surgeries. These may be modified on a case-to-case basis depending upon the presence of concurrent patient risk factors for VTE (Table 1).

S. No.	Type of Robot-assisted Surgery	Early Postoperative Ambulation	Mechanical Thromboprophylaxis	Pharmacologic Thromboprophylaxis (PTP) LMWH	Extended PTP (after hospital discharge)
1	Radical Prostatectomy	+	+	+	Not required
2	Radical Cystectomy	+ If possible	+	+	Not required
3	Radical Nephrectomy	+	+	Not required for Partial Nephron Sparing Nephrectomy. Required for total radical nephrectomy	Not required
4	Radical Hysterectomy	+	+	Not Required	Not required
5	Radical Adrenalectomy	+	+	Not Required	Not Required
6	Radical Osophagectomy	May not be possible	+	+	+

**Table 1:** VTE following robot-assisted abdominopelvic surgery.

A 2008 NIS review of major abdominal operations showed an overall VTE rate of 1.5%. The incidence of VTE following nephrectomy is low and poorly studied, out of which majority occur after discharge. In a recent study, it was found that operative time is most predictive of VTE following radical nephrectomy and advanced age is most predictive following partial nephrectomy [16]. Risk stratification is the key deciding factor for the type of prophylaxis given. According to the AUA (American Urological Association) [17], high risk laproscopic and robotic cases may require pharmacologic prophylaxis in addition to mechanical prophylaxis. The major point of debate is the duration of thromboprophylaxis required. Even though robotic surgeries are associated with minimal blood loss, there is still a

theoretical chance of torrential hemorrhage, especially when dissecting along neurovascular planes. The estimation of blood loss can be difficult and this problem may be compounded by the concurrent use of pharmacologic thromboprophylaxis. The Caprini and the Rogers score [18] are used for risk assessment for VTE in surgical patients. In these, various patient/surgical risk factors are given different points and the total score obtained by adding these points determine the overall risk of development of VTE. These scoring systems need to be modified for robotic surgeries. The Khorana score [19] is used for evaluation of VTE risk in cancer patients. It assigns 2 points to cancer at very high risk sites (pancreatic or gastric) and one point to cancer at high risk sites (lung, ovarian or bladder). Further, 1 point is given to

each of the following factors: platelet count  $>350 \times 10^9/L$ , hemoglobin  $<10 \text{ g/dl}$  and/or use of erythropoietin-stimulating agents, leukocyte count  $>11 \times 10^9/L$  and body mass index  $>35 \text{ kg/m}^2$ . Patients with a score  $\geq 3$  are at high risk for developing VTE.

Newer risk factors specific to robotic surgeries should be incorporated for accurate risk assessment. These include the long operative times due to learning curve of this novel surgical technology, prolonged pneumoperitoneum, steep trendelenberg positioning, lithotomy position and restricted fluid therapy. In a scientific paper published by Abel et al. [20], prolonged operative time was found to increase the risk of VTEs after robot-assisted radical prostatectomy. Further research is required validating the risk factors for VTE in robotic surgeries. Venous stasis (part of the Virchow's triad [21]) is one of the most important factors in the development of thromboembolism. Theoretically, prolonged pneumoperitoneum can increase the intra-abdominal pressures and compress the vessels. This can be compounded by extremes of positioning required for robotic surgeries. In pelvic surgeries (urologic and gynaecologic robotic surgeries), the lower limbs are abducted and flexed at the hips to accommodate the robot in between the two legs and placed in specially-designed lithotomy poles. This can compress the femoro-popliteal vessels, increasing the risk of DVT if placed in this position for a long time. In addition, intra-operative intravenous fluid therapy is restricted [22] in most robotic surgeries so as to minimize surgical oozing and tissue congestion. This can also lead to hemo-concentration and cause venous stasis temporarily. All these risk factors put together can increase the risk of VTE, if robotic surgery is being performed for cancer or in patients with significant comorbidities (which by itself increases the risk of DVT). On the other hand, there are several advantages [23] of robotic surgeries which can prevent the development of VTE, like less postoperative pain, early return to activity, minimal immobilization, shorter hospital stay and decreased transfusion requirements. The decision to give pharmacologic prophylaxis should be taken on an individual patient basis, as it is associated with increased risk of bleeding and thrombocytopenia. Nevertheless, mechanical thromboprophylaxis should be used in all robotic surgeries, especially robot-assisted abdomino-pelvic surgeries in the entire perioperative period. Even though they have the distinct advantage of not increasing the bleeding risk, they are not shown to decrease the risk of PE or death (Table 2) [24].

S. No.	Advantages of Robot-assisted surgery reducing VTE risk
1	Early return to activities of daily living (DALY); faster postoperative mobility
2	Lesser postoperative pain with reduced analgesic requirements
3	Lesser intra-operative blood loss and shorter hospital stays
4	Reduced requirements of blood or blood product transfusions
5	Patient selection for robotic surgery with early stage of cancer

**Table 2:** Suggestive positive factors associated with reduced incidence of thrombosis following robotic surgery.

Robotic-assisted radical prostatectomy (RARP) has recently become the leading option for the treatment of localized pancreatic carcinoma. The Pasadena Consensus Panel (PCP) [25] convened in California (2011) recognized a number of factors influencing recovery of sexual function and continence following prostate surgery. The

transperitoneal RARP is more commonly employed and is advantageous in patients requiring pelvic lymph node dissection. They opined that the use of medical DVT prophylaxis is optional and clinicians should follow NICE or other national guidelines. A recent study by done Chalmers, et al. [26] concluded that the risk of VTE in patients undergoing robotic prostatectomy is low and not significantly decreased with prophylactic heparin plus sequential compression devices (SCDs) compared with SCDs alone. In another study done by Leyh-Bannurah, et al. [27], blood loss, transfusion rates and 90-day complication rates were assessed in patients receiving ongoing 100mg/day aspirin medication and undergoing open radical prostatectomy (RP) or RARP. In this study, all patients received LMWH prophylaxis. They concluded that both RP and RARP can be safely performed in patients with ongoing aspirin medication without greater blood loss. Dextran [28] as an intravenous fluid was found to halve the risk of DVT and PE, irrespective of the type of surgery, but at the cost of increased bleeding.

Regional anesthetic techniques must be employed whenever feasible as they provide a certain degree of protection against DVT in comparison to general anesthetic techniques. Apart from decreasing the intraoperative anesthetic requirements and providing postoperative analgesia, epidural catheter insertion also contributes to VTE prophylaxis by preventing hypercoagulability [29].

Specific VTE risk factors have been identified in patients undergoing RARP, which have been elucidated in the following Table 3 [30].

S.N o.	Patient related VTE risk factors	Surgery-related VTE risk factors
1	Active cancer or cancer treatment	Total anesthetic and surgical procedure time $>90$ minutes
2	Age $>60$ years	Total procedure time $>60$ minutes with surgery involving pelvis or lower limbs
3	Known thrombophilia	Expected substantial reduction in mobility
4	Obesity	
5	Significant comorbidities (eg. Cardiac, metabolic, endocrine or respiratory pathologies)	
6	Personal or Family (first degree relative) history of VTE	
7	Use of hormone replacement therapy	
8	Varicose veins with phlebitis	

**Table 3:** Risk factors for VTE specific to robotic surgery.

Anesthesia-specific factors for VTE, like use of general anesthesia alone or general plus regional anesthetic techniques and the use of Dextran (which reduces risk of DVT by half) as an intravenous fluid, can be added to the above table for completeness.

The risk of developing VTE following robotic gynecologic oncology is reported to be low [31]. In a recent retrospective study done at the Feinberg school of Medicine, Chicago found that there were no cases of VTE after hospital discharge among patients undergoing robotic endometrial cancer surgery without

pharmacologic prophylaxis. It was concluded by Neubauer et al. that patients undergoing a minimally invasive surgical procedure are at lower risk of postoperative VTE as compared to those undergoing an open laprotomy [32]. Hence, in view of the costs and risks associated with the use of LMWH as well as the low incidence of VTE among these patients, extended pharmacologic prophylaxis may not be required for women undergoing robotic radical hysterectomy. It must be remembered that, this observation cannot be extrapolated to all patients and all robotic surgeries. Patient-related factors, stage of cancer, body mass index, extent of lymph node dissection and duration of surgery must be considered in determining the risk of developing VTE. Of special importance in the prevention of VTE following robotic-assisted surgeries is the routine perioperative use of mechanical thromboprophylactic devices and encouragement of early postoperative mobility [33]. In addition, these patients can be put on prophylactic LMWH or one of the newer oral anticoagulants till the duration of hospital stay, especially in high risk cases.

### Precautions Following Thromboprophylaxis during Robotic Surgery

Institution of pharmacologic prophylaxis puts the patient at increased risk of epidural hematoma [34] if regional anesthesia is planned along with general anesthesia for robotic surgery. Usually epidural blocks are not required for routine robotic surgeries. Multimodal pain management using systemic analgesics (paracetamol, non-steroidal anti-inflammatory agents and opioids) and local anesthetic port-site infiltration generally suffice after most robotic procedures. Further, ultrasound-guided TAP (transversus abdominis plane) block [35] can provide excellent analgesia in the postoperative period. TAP blocks can be safely given in patients receiving pharmacoprophylaxis. In certain robot-assisted cancer surgeries with associated open component (radical cystoprostatectomy and bladder reconstruction with ileal conduit or neobladder formation and retroperitoneal lymph node dissections), epidural catheters may be inserted pre-induction for perioperative analgesia. In such circumstances, the administration of pharmacologic prophylaxis needs to be cautious and standard ASRA (American Society of Regional Anesthesia) guidelines [36] should be strictly followed. If UFH is chosen, then a gap of at least 4 hours should be given between dosing and catheter placement. If LMWH is administered for thromboprophylaxis, the interval should be at least 10-12 hours. There is no contraindication to continuing aspirin for epidural catheter insertion. In patients on Fondaparinux, epidural placement is better avoided. Care also needs to be taken during catheter removal by adjusting the heparin dose interval. A close watch should be made in the postoperative period for the development of epidural hematoma.

### Future Perspectives

Robotic surgery is the future of minimal access surgery. With the advancements in surgical technology, newer aspects of patient safety must be addressed on priority basis. Venous thromboembolism continues to increase patient morbidity and mortality in the perioperative period, especially in cancer patients. Recent studies have demonstrated a reduced incidence of VTE following robotic surgery. But this needs to be validated by evidence-based medicine and consensus guidelines must be developed on the type and duration of thromboprophylaxis required. Specific research must focus on cancer patients undergoing robotic radical surgery, as their risk of developing VTE is significantly higher than the general population.

Chemotherapeutic agents with lower risk of thrombosis may be preferred, if possible. One important aspect unique to robotic surgery is that once the robot is docked, it is difficult to de-dock in the event of a crisis situation. All the involved operation theatre personnel must be well-versed in emergency de-docking of the robot [37] in an emergency scenario. Intra-operative pulmonary embolism needs prompt recognition and expeditious action. Regular drills and training programs must be conducted for recognizing a crisis situation during any stage of robot-assisted surgery and as well as in quick de-docking of robotic instruments inserted into the patient. Stimulation based learning can be of immense help in this regard. The future also calls for specialized training of anesthesiologists in conducting various types of robotic surgery. As the surgical operative times decrease with the improvement in learning curve of the surgeons, the incidence of VTE may also decrease with time. Early ambulation in the postoperative period must be incorporated as a routine practice whenever feasible after robotic surgery to minimize the risk of DVT. Apart from the already existing mechanical thromboprophylactic devices, newer devices may be developed which can definitively prevent VTE in the perioperative period. All patients must be thoroughly educated about the symptoms of DVT and PE after discharge from the hospital.

### Conclusions

Thromboembolism continues to be a devastating perioperative complication, increasing patient morbidity and mortality. Since the advent of minimally-invasive surgery, the incidence of postoperative VTE has reduced. Robotic surgery is a fairly recent advancement which provides several advantages like three-dimensional view, dexterity similar to human hand, early patient recovery, less postoperative pain and minimal blood loss. Separate risk assessment strategies must be employed for determining VTE risk in patient undergoing robotic-assisted surgeries. The decision to administer pharmacologic thromboprophylaxis must be taken on an individual patient basis, by carefully weighing the risk-benefit ratio in each case. This is especially true for cancer patients. Further multi-center, large-scale randomized controlled trials are needed to reach a consensus guideline on VTE risk assessment and prophylaxis for different types of robotic surgeries. Nevertheless, mechanical thromboprophylaxis must always be used in all patients of robotic surgery in the entire perioperative period, with special emphasis on early postoperative mobilization. The ultimate goal is to prevent DVT and PE, so as to ensure a successful and safe robotic surgery program.

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