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The perioperative management of patients with gynaecological cancer undergoing major surgery: A debated clinical challenge

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Contents

Abstract

Major extensive surgery still represents a cornstone of therapy of gynaecological cancer, and the adoption of implemented clinical guidelines for perioperative management can significantly decrease patient morbidity and mortality and reduce hospital stay. The overall risk of deep venous thrombosis in patients undergoing gynaecological surgery ranges from 7% to 45%, and fatal pulmonary embolism occurs in approximately 1% of these women. A meta-analyses of randomised trials showed a significant decrease in deep venous thrombosis in women receiving unfractioned heparin [UFH] compared with controls, and revealed no significant difference in deep venous thrombosis and pulmonary embolism between patients who received UFH and those who received low-molecular weight heparin [LMWH]. Potential advantages favouring LMWH over UFH include once-daily versus repeated daily injections and a lower risk of heparin-induced thrombocytopenia. All patients undergoing major surgical operations should receive LMWH that should be started preoperatively and then given for 7–10 days at least and prolonged for up to 4 weeks in high-risk cases. Antithrombotic mechanical methods can be added to pharmacological agents, but should not been used alone. Cephalosporins and amoxicillin–clavulanic acid have been widely used in gynaecological surgery prophylaxis. Both amoxicillin–clavulanic acid and cefazolin have good *in vitro* activity against the microbes more frequently involved in postoperative infections, such as Gram-negative bacilli, but amoxicillin–clavulanic acid is more effective against anaerobes. A single dose of antibiotics has been shown to be as effective as multiple doses in many trials that have compared a single-dose regimen with a multiple-dose regimen. Amoxicillin–clavulanic acid prophylaxis at the induction of anaesthesia can be suggested for gynaecological cancer patients undergoing major gynaecological surgery with or without colorectal resection. An additional antibiotic dose is recommended for prolonged operations or when intraoperative blood loss is important. Cephalosporins can be administered to women with a history of penicillin allergy not manifested by an immediate hypersensitivity reaction, whereas tigecyclin should be reserved to patients with a prior anaphylactic reaction to beta-lactams. Recent meta-analyses of randomised trials on patients undergoing elective colorectal surgery found more anastomotic leakages in patients who had preoperative mechanical bowel preparation with oral administration of different solutions than in those who had not, whereas there were no significant differences between the two arms as for wound infections, other septic complications, and non-septic complications.

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Therefore, preoperative mechanical bowel cleansing is not warranted for gynaecological cancer patients scheduled for surgery that may involve colon–rectum. After major abdominal gynaecological surgery, early oral feeding (within the first 24 h regardless of the resolution of postoperative ileus) appears to be associated with increased nausea, shorter time to the presence of bowel sound, shorter time to first solid diet, and a trend toward shorter hospital stay when compared with delayed feeding. Since early oral feeding is safe but associated with increased nausea, the decision whether to adopt this postoperative regimen should be individualised. Decision making processes about thromboprophylaxis, antibiotic prophylaxis, bowel preparation for surgery that may involve colon–rectum, and timing of postoperative oral feeding will become more and more relevant for improved safety and quality of life of women with gynaecological cancer.

Keywords: Thromboprophylaxis; Antibiotic prophylaxis; Gynaecological surgery; Postoperative oral feeding; Bowel preparation for surgery

1. Introduction

In last years many efforts have been made to establish an evidence-based approach to the therapy of patients with gynaecological cancer, combining the modalities of surgery, chemotherapy, and radiation. The decrease of complications and early and late side effects have become more and more important clinical issues in the treatment planning, in addition to improving survival through surgical technology, multicenter randomised trials, and novel molecularly targeted therapies. Major extensive surgery still represents a cornstone of therapy, and the adoption of implemented clinical guidelines for perioperative management can significantly decrease patient morbidity and mortality and reduce hospital stay. Therefore, decision making processes about thromboprophylaxis, antibiotic prophylaxis, bowel preparation for surgery that may involve colon–rectum, and timing of postoperative oral feeding will become more and more relevant for improved safety and quality of life of women with gynaecological cancer.

2. Venous thromboembolism

2.1. Thrombosis in cancer patients: pathogenesis and epidemiological data

Cancer is a model of acquired thrombophilic condition, and approximately 50% of all patients and up to 95% of those with metastatic disease present some abnormalities of haemostatic parameters [1–5]. The pathogenesis of thrombosis is mainly related to both the direct procoagulant activity of substances released by tumour cells (tissue factor [TF] and cancer procoagulant [CP]), and the interaction between tumour cells, monocytes/macrophages, platelets, and endothelial cells [6–11] (Table 1). TF is a transmembrane receptor lipophilic phospholipoprotein constitutively expressed in different human malignancies [6,7]. Moreover, adhesion receptors on tumour cells may bind and activate monocytes/macrophages which on turn generate TF. This factor activates the extrinsic pathway of coagulation cascade by binding and activating factor VII [FVII] and increasing the activity of activated FVII (FVIIa), thus leading to catalysis of factor X [FX] to FXa and of prothrombin to thrombin [6]. CP is a single-chain Vitamin K-dependent cysteine protease expressed in several human malignancies, that can directly activate FX [9] and induce dose-dependent platelet activation [10]. Tumour cells can release inflammatory cytokines, such as tumour necrosis factor [TNF] and interleukin-1 [IL-1], which induce the expression of TF and down-regulate that of thrombomodulin in vascular endothelial cells, thus converting the normal anticoagulant endothelium into a prothrombotic endothelium [11]. Anticancer therapy may itself contribute to the prothrombotic state [12–15].

Table 1
Factors predisposing to thrombosis in cancer patients.

(1) Release of tissue factor and cancer procoagulant by tumour cells
(2) Interaction between tumour cells, monocytes/macrophages, platelet and endothelial cells
(3) Venous stasis due to compression by tumour masses and patient immobilization
(4) Anticancer treatments (surgery, chemotherapy, hormotherapy, molecularly targeted-therapy, irradiation)

Thrombotic events are especially common in cancer surgical patients [16]. Factors influencing the thrombotic risk include old age, prolonged duration of anaesthesia, prolonged postoperative immobilization, and previous history of venous thromboembolism [16,17]. All cancer patients undergoing major surgery, defined as laparotomy, laparoscopy, or thoracotomy lasting greater than 30 min, are considered at high risk for the development of venous thromboembolism by the American Society of Clinical Oncology [ASCO] [18].

Chemotherapy itself is associated with two to sixfold increased risk of venous thromboembolism, probably due to drug-induced endothelial damage, release of inflammatory cytokines, increase in TF expression in monocytes/macrophages and endothelial cells, and decrease in plasma protein C and protein S levels [19–21]. For instance, paclitaxel enhances thrombin-induced TF expression in human endothelial cells in a concentration- and time-dependent manner via c-Jun terminal NH2 kinase activation [21].

According to the ASCO guidelines, hospitalized patients with cancer should be considered candidates for prophylaxis with anticoagulants in the absence of bleeding or other contraindications to anticoagulation [18]. Routine prophylaxis with antithrombotic agents is not suggested for ambulatory cancer patients who are giving chemotherapy because