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Thromboprophylaxis in gynecologic cancer surgery: Is extended prophylaxis with low molecular weight heparin justified?

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ABSTRACT

Objective: Evidence on the optimal duration of thromboprophylaxis with low molecular weight heparin after gynecologic cancer surgery is scarce and the benefits of extended prophylaxis have not been validated specifically in these patients. The aim of this study is to assess the efficacy and safety of postoperative venous thromboembolism (VTE) prophylaxis with enoxaparin 40 mg for 28 days, as recommended by international guidelines, compared to 7 days in patients undergoing surgery for gynecologic cancer.

Study design: Prospective cohort study compared to a historic cohort of women who underwent surgery for gynecologic cancer in our center between 2004 and 2014. Pre- and postoperative screening with a routine duplex scan was done in the prospective cohort. Comparative analysis of comorbidity, surgical technique and incidence of VTE, as well as prognostic factors of events and mortality.

Results: N:571 patients (28 days: 207, 7 days: 364). No significant differences were identified between groups in regard to the factors related to VTE in our series. There were no differences in VTE incidence between groups after one month (1.9% vs 1.4%; $p = 0.729$), 90 days (2.4% vs 2.5%; $p > 0.99$) or during follow-up (Breslow $p = 0.156$). No deaths due to VTE at 90 days were recorded. Only one case of asymptomatic DVT was identified in the screening with duplex. The incidence of postoperative bleeding was similar in both groups (0.5% vs 2.2%; $p = 0.166$). The presence of a history of VTE was the only independent risk factor for VTE after one month (OR 14.31 CI 95% 2.67–76.87; $p = 0.002$) and 90 days (OR 8.27 CI 95% 1.65–41.45; $p = 0.010$). No differences were identified regarding age, other comorbidities, type of tumor, stage, surgical approach, reintervention or adjuvant therapy in the multivariate analysis.

Conclusion: Extended prophylaxis for 28 days with enoxaparin did not improve the rates of VTE following gynecologic oncological surgery in our series compared to the 7-day therapy, although neither was this extended duration associated with adverse events or mortality.

Introduction

Despite the advances made in recent years, venous thromboembolism (VTE) still involves high morbidity and mortality rates, and it is the most frequent preventable cause of in-hospital death in the United States [1]. One third of these deaths occur in patients with a history of recent surgery [2], whereas the presence of cancer increases the risk of VTE 4–7 times with respect to the general population, making it the second cause of death in these patients [3]. Therefore, patients undergoing a surgical intervention due to a gynecologic malignancy, present a high risk of VTE due to both risk factors. In these cases, a reduction of its incidence has been demonstrated using thromboprophylaxis with low molecular weight heparin (LMWH) [4].

However, despite the consensus regarding the benefits of LMWH use in patients with gynecological cancer, the optimal duration of this treatment has not been determined yet. The recommendation from some guidelines for prophylaxis with

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LMWH during 28 days for all patients who undergo abdominal and pelvic surgery for oncological diseases [4] has not been validated specifically in gynecologic oncological surgery, and no randomized trial assessing the benefits of different durations of prophylaxis in this population has been conducted.

Therefore, given the low quality of the evidence on extended prophylaxis with LMWH following gynecologic oncological surgery, we designed this study to assess the efficacy and safety of postoperative VTE prophylaxis with enoxaparin 40 mg for 28 days compared to 7 days in patients undergoing surgery for a gynecologic cancer, as well as the incidence and prognostic factors for VTE in this kind of patients.

Materials and methods

Following the implementation of prolonged prophylaxis until 28 days in our center, a prospective cohort study was designed including all patients with gynecological cancer undergoing surgery at the Hospital Clinico San Carlos between 2012 and 2014 (28d group), that were compared to a historic cohort of patients who underwent the same type of surgery between 2004 and 2011 who had followed a 7-day thromboprophylaxis regime (7d group). The protocol of this study EMCOG: ("thromboprophylaxis with Enoxaparin for a Month following Gynecologic Oncological Surgery") was submitted and accepted by the ethics committee of our hospital and the "Agencia Española del Medicamento" (Spanish Drug Agency) and all the patients signed an informed consent.

Women who had undergone surgery for a gynecologic cancer with laparotomy, laparoscopy or robotic surgery at our site throughout this period, and who signed the informed consent were included in the study. Patients having surgery for vulvar cancer or benign pathologies were excluded, as well as those with a contraindication for anticoagulation, concomitant anticoagulant treatment, history of VTE in the previous six months, severe kidney disease (defined as creatinine clearance lower than 30 ml/min) and pregnant women.

All patients who met the inclusion criteria underwent a duplex scan of the lower limbs before surgery, excluding from the study those who presented with deep vein thrombosis (DVT) at that moment. The patients included were initiated on enoxaparin 40 mg, 12 h before surgery and during 28 days afterwards, with a follow-up duplex scan carried out one month after surgery (Fig. 1).

Data from both groups was collected in a dedicated database including demographic and preoperative clinical characteristics, comorbidities, cancer staging and other data related to their pathology and treatment, including chemo- and radiation therapy, cancer recurrence and survival. Similarly, variables related to the surgical intervention were also recorded. DVT and pulmonary embolism (PE) episodes were recorded at the follow-up visits and by reviewing the medical records of all the episodes of admission to the emergency room and all the lower limb duplex scans, scintigraphies and CT angiograms carried out in these patients during that period. A comparative study was conducted between groups studying the incidence of thromboembolic disease and adverse events after 30 days, 90 days and during follow-up, as well as mortality in these patients. Subsequently, a uni- and multivariate analysis was carried out to assess the independent risk factors related to these outcomes in both groups.

Baseline characteristics and comorbidities along with intraoperative data were compared between the two groups using Pearson chi-square or Fisher's exact tests for discrete variables and the unpaired Student's *t*-test for continuous variables. The early outcome endpoints: VTE incidence and hemorrhagic complications after 30 and 90 days, were compared by multivariate analysis using a logistic regression model. Outcomes during follow up including freedom from VTE and survival were compared using Kaplan-Meier life table analyses, Breslow test, and Cox proportional hazards model. Independent risk factors related to these early and late outcomes were studied with a univariate analysis by Chi-square test and Cox proportional hazards model. Covariates with P value <0.05 in this univariate analysis were included in the multivariate analysis by logistic regression and Cox proportional hazards model. Backward stepwise selection was applied to

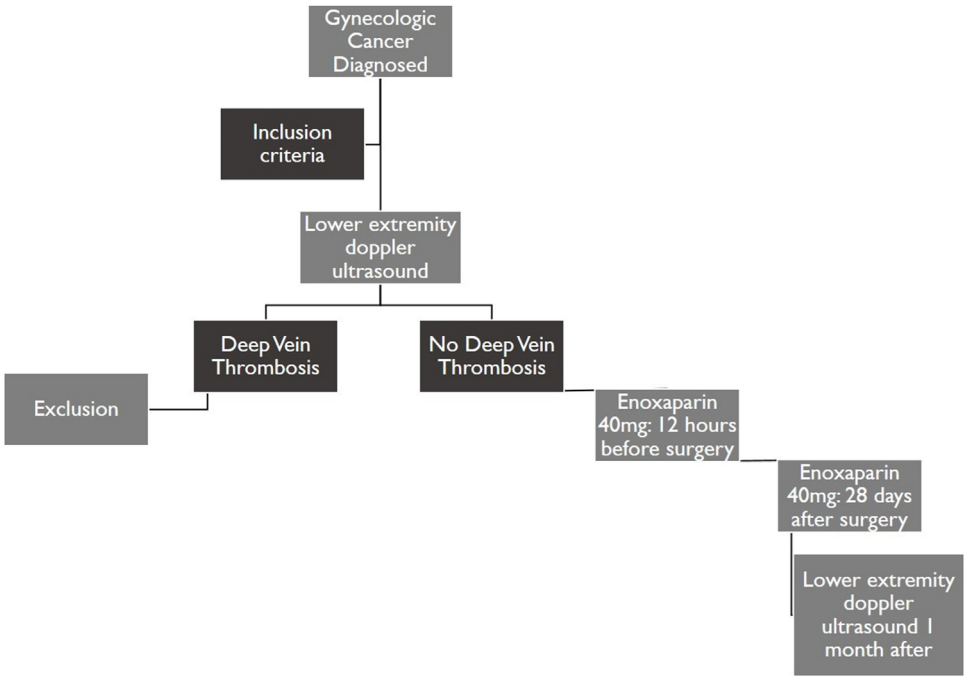

Fig. 1. Study design: Management of included patients.