Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: A randomised prospective double-blind clinical study

C. Baykal, A. Al, E. Demırtaş, A. Ayhan

Department of Obstetrics & Gynaecology, Hacettepe University School of Medicine, Ankara (Turkey)

Summary

Objective: This study aimed to compare the haemorrhagic complications and efficacy of enoxaparin, a low molecular weight heparin (LMWH), and conventional standard heparin (SH) in gynaecological oncologic surgery.

Materials Methods: A double blind, randomised trial was performed on 102 consecutive women undergoing gynaecologic cancer surgery with pelvic and paraaortic lymphadenectomy. The women were separated into those who were given 2,500 IU enoxaparin once daily and SH in a dose of 5,000 IU three times daily. The groups were analysed for intraoperative blood loss, drainage, transfusion requirements, perioperative haemoglobin decrease, wound haematoma, and clinical deep venous thrombosis.

Results: The two groups were well matched for age, weight, and other factors, which could predispose to the development of deep venous thrombosis (DVT) and haemorrhage. No patient developed clinical significant DVT, wound haematoma or intra-abdominal bleeding. There was no significant difference in bleeding complications between the two regimens. The antiFXa level in the plasma was correlated strongly with patient weight.

Conclusions: A dose of 2,500 IU enoxaparin/day does not cause more bleeding complications than SH 5,000 IU three times daily when used to prevent thrombosis. However, the dose of enoxaparin must be adjusted to the patient's weight.

Key words: Enoxaparin; Gynaecologic oncology; Haemorrhage; AntiFXa.

Introduction

Low molecular weight heparin (LMWH) is widely used in abdominal and orthopaedic surgery because of their prophylactic characteristics and pharmaceutical advantages over standard heparin (SH). It has been shown that LMWH is as effective and reliable as low dose SH in cases that underwent major abdominal surgery and orthopaedic surgery carrying risks of deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) [1-10]. In previous reports, LMWHs were compared with SH and other prophylactic modalities in gynaecology [3, 11, 12]. However, the guidelines are controversial for gynaecologic oncology cases [13]. Gynaecologic surgery performed for genital cancers carry not only the risk of thrombosis but also the risk of retroperitoneal bleeding complications because lymphatic debulking is routinely performed. Some publications report that LMWHs cause more bleeding complications than SH while others indicate the opposite [1, 5, 7, 10-12, 14-16].

AntiFXa and antiFIIa levels are measured in plasma and show the inhibition rate of FXa and FIIa by heparin and LMWHs. SH inhibits FXa together with FII through a coagulation cascade. However, LMWHs have a higher ratio of antiFXa to antiFIIa activity. AntiFXa levels are correlated with weight [17]. Studies with LMWHs were performed using body weight-adjusted doses or fixed doses. However, it is unclear from a pharmacokinetic and clinical point of view, whether body weight adjustment of LMWHs are really necessary for prophylaxis or the treatment of acute DVT [18-20]. In general, a fixed dose of subcutaneous 2,500 antiFXa is recommended for prophylaxis in general surgery and orthopaedic surgery [5, 7-10, 13].

The aim of this study was to compare the haemorrhagic complications between fixed doses of subcutaneous 2,500 antiFXa units enoxaparine (a LMWH) (Clexan-Eczacıbaşı-Rhoune Poulenc, Turkey) and conventional doses of SH (3 x 5,000 U subcutaneously) in cases that underwent pelvic and paraaortic lymph node dissection for gynaecologic cancers. A secondary objective was to analyse the correlation of plasma antiFXa levels with the weight of the patients.

Materials and Methods

The study was performed on 102 consecutive patients who were admitted to the gynaecologic oncology service between 1998 and 1999. The patients were between 40-70 in age, nonsmokers and free of any history of peripheral arterial disease or thrombosis. Patients who had any diagnosed coagulation defects (bleeding diathesis, prolonged activated partial thromboplastin time (aPTT) or prothrombin time (PT), platelet count <100,000, low antitrombin III level, chronic liver disease, etc.), used oral anticoagulants/heparin in the previous six weeks, received hormone replacement therapy in the previous six months or had a heparin allergy were excluded. Patients who underwent vulvectomy were also excluded because of the long immobilisation time. All patients signed an informed consent.

This study was sponsored by Eczacıbaşı-Rhoune Poulenc, Turkey

Revised manuscript accepted for publication January 8, 2001

The patients who corresponded the inclusion criteria were randomised into two groups by the gynaecologic oncology team. The surgical team and those collecting laboratory and clinical data were not informed about the prophylactic anticoagulation method being used. The first patient group received 2,500 antiFXa units of enoxaparin 0.4 ml (Clexane-Eczacıbaşı-Rhoune Poulenc, Turkey) two hours before the operation and then once every 24 hours. The second group received 5,000 U SH every eight hours. All of the injections were performed subcutaneously on the abdominal wall. All of the patients were operated under general anaesthesia by the same surgeon and, paraaortic lymph node dissection up to the level of the left renal artery with bilateral pelvic lymph node dissection were performed. A sump drain catheter was placed into the Douglas pouch in every patient.

Clincal and laboratory findings were recorded daily. Clinical variables were determined as amount of bleeding during operation, operation duration, intraoperative and postoperative blood transfusion, amount of drainage quantity, wound haematoma, intra-abdominal bleeding, and hospitalisation duration. A complete blood count, aPTT and antiFXa levels were measured 4-6 hours after the operation and on the 1st, 2nd, 3rd, and 7th days postoperatively. AntiFXa levels on days 1, 2, 3 and 7 were measured four hours after the injection of enoxaparin.

No screening test was used for diagnosing DVT. Any patient suspected of DVT was examined by duplex ultrasonography and if required venography; for PTE, by ventilation-perfusion scan and pulmonary arteriography.

AntiFXa level measurements were performed automatically by STA® (Rothachrom® HBPM/LMWH) compact system (Diagnostica, Stago, France) after all the patients' plasmas were stored at –20°C. Other tests such as haemoglobin and coagulation tests were performed daily.

Statistics

Demographic and clinical factors were compared between groups using the Chi-square, paired t-test and Mann-Whitney U tests when appropriate. The differences between daily antiFXa levels were tested by analysis of variance. Pearson's correlation analysis was used to show the probable relation between body weight and antiFXa level. The statistical analysis was performed with SPSS (Release 9.0, Chicago, Illinios) packet program.

Table 1. — *Clinical characteristics.*

		Enoxaparin	SH	*p*
Age*		56.9±10.3	57.8±9.6	ns†
Body-weight*		66.5±12.4	66.3±13.2	ns
BMI				ns
	< 20	3 (55.3%)	4 (7.3%)	
	20-25	26 (55.3%)	31 (56.4%)	
	26-30	13 (27.7%)	14 (25.5%)	
	>30	5 (10.6%)	6 (10.9%)	
Medical history				ns
	ASCD	6 (12.8%)	7 (12.7%)	
	HT	9 (19.1%)	11 (20.0%)	
	DM	6 (12.8%)	8 (14.5%)	
	Other	5 (10.6%)	7 (12.7%)	
Tumor region				ns
	Ovary	23 (48.8%)	24 (43.6%)	
	Endometrium	10 (21.3%)	16 (29.1%)	
	Cervix	14 (14%)	15 (27.3%)	

*mean ± standard deviation; † statistically insignificant; BMI, body mass index; ASCD, atherosclerotic cardiac disease; HT, hypertension; DM, diabetes mellitus.

Table 2. — *Clinical and laboratory findings of the operation and bleeding complications.*

	LMWH	SH	*p*
Type of surgery			ns*
TAH+BSO+BPLND+ PALND+omentectomy	33 (70.2%)	40 (72.7%)	
Type III Hysterectomy+ BPLND+PALND	14 (14%)	15 (27.3%)	
Anaesthesia duration (hour)†	2.51±0.7	2.44±0.6	ns
Intraoperative blood loss†	915.5±399.9	798.4±535.3	ns
Blood transfusion (unit)†			ns
Intraoperative	1.43±1.4	1.2±1.4	
Total	3.2±1.8	2.6±2.2	
Decrease in hematocrit†	10.3±3.2	7.6±4.7	ns
Drainage†	836.8±533.2	723.2±543.7	ns
Hospitalisation duration†	9.7±3	9.44±2.9	ns

*Statistically insignificant; †mean ± standard deviation; TAH, total abdomical hysterectomy; BSO, bilateral salpingo-oophorectomy; PALND, paraaortic lymph node dissection; BPLND, bilateral pelvic lymph node dissection.

Results

One hundred and two consecutive patients were included in the study; 47 of the patients underwent surgery for ovarian cancer, 29 for cervix cancer, 26 for endometrium cancer. Nine patients were excluded from the study (five patients had received HRT, two had chronic liver disease, two had mobilisation restrictions). Forty-seven patients received enoxaparin and 55 patients SH as described above. No significant difference was found between groups with respect to age, body weight, body-mass index, tumor type or accompanying diseases (Table 1).

Type of operation, duration of anaesthesia and hospitalisation were similar between the groups (Table 2). Intraoperative bleeding, intraoperative and total blood transfusion rates, decrease in hematocrit on the first day postoperatively and amount of drainage from catheters were higher in the LMWH group, however these differences were not statistically significant. There were no demonstrated DVT, PTE, wound haematomas or postoperative haemorrhagia in either group.

No statistical difference was found between antiFXa levels on the 1st, 2nd, 3rd or 7th days. However, a strong reverse correlation was found between body weights and average antiFXa levels (Pearson correlation = –0.811, $p < 0.01$). When patients were grouped by body weight the rate of patients with antiFXa levels below the effective level in every group can be seen in Figure 1 (effective antiFXa level was accepted as 0.05 IU/ml).

Discussion

In general surgery and orthopaedic surgery, LMWHs have been shown to be as equally effective and safe as SH for prophylaxis of thrombosis [1-10]. Previously, LMWHs were reported as effective and reliable as low-dose SH in gynaecologic surgery [5, 10-12]. However, data evaluating the reliability of LMWH in high risk

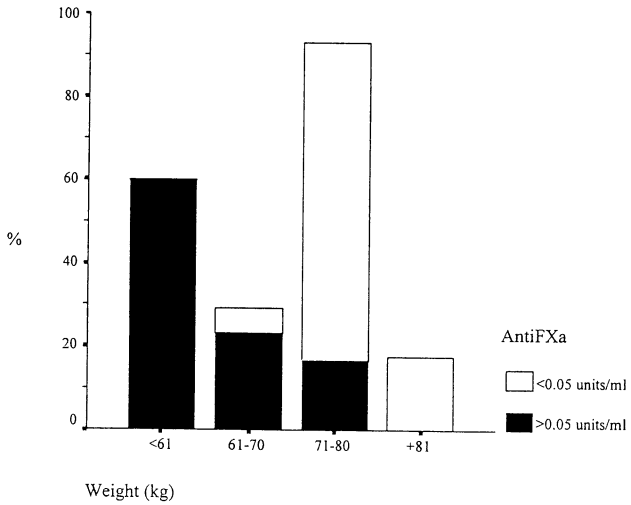

Figure 1. — Rate of the patients' effective anticoagulant dose not achieved.

gynaecological surgery are insufficient today [13]. In gynaecologic oncology, low dose heparin or interrupted pneumatic compression for at least five days is recommended for effective thromboprophylaxis for high risk patients [13]. The current study reports a group of patients who underwent gynaecologic cancer surgery. In the literature there was no such series with only gynaecologic malignancy patients.

In the study no bleeding or thrombosis complications were observed. However, although it was not found to be statistically significant, enoxaparin tends to cause bleeding more than SH does. Bleeding risk is controversial when LMWH is compared with SH [1, 7, 14]. However, in most studies, LMWH generates fewer bleeding complications than SH [3-6, 12, 15, 21-23]. In gynaecology studies, DVT is observed as much as 40% in the screening studies performed with fibrinogen marked with iodine-125 for venography. However, symptomatic DVT incidence either with low-dose SH prophylaxis or without prophylaxis is fairly low (1-2%). Clinically symptomatic DVT and PTE were not observed in patients in either group. Sample size was small to assess the prophylactic effects of LMWH for PTE or DVT.

As reported previously, daily antiFXa levels during enoxaparin injections were stable and a strong reverse correlation between antiFXa activity and patient weight was found. Levine *et al.* reported that the incidence of postoperative thrombosis was low (6.3%) if the minimum antiFXa level exceeded 0.1 units per ml, but increased to 18.8% if the anti-factor Xa level was less than or equal to 0.05 units per ml [24]. They stated that when enoxaparin is administered once daily subcutaneously, the 12-hour antiFXa level should not exceed 0.2 units per ml to minimise bleeding, and levels greater than 0.05 units per ml should be obtained for optimum efficacy [24]. In the study, as body weight increases the rate of patients with insufficient antiFXa activity also increases when the lowest effective antiFXa activity was accepted as 0.05 IU/ml (Figure 1). All of the studies in experimental animal models and in patients receiving low molecular weight heparin (LMWH) to prevent thromboembolic events after surgery have not demonstrated a clear relationship between antiFXa and antiFIIa activities in plasma and either bleeding or prevention of thrombosis [25]. On the other hand, it is unclear whether weight adjustment of LWMH is really necessary for treatment or prophylaxis. Recently, it has been reported that fixed dose subcutaneous LMWH was at least as efficacious as SH in resolving acute DVT [18-20]. However, the evidence suggests that antiFXa levels could predict bleeding or thrombosis. In our opinion, this relation should be considered when bleeding or thrombosis risks are evaluated.

In conclusion, 2,500 antiFXa units of enoxaparin can be used prophylactically in gynaecologic oncology surgery without causing any significant increase in bleeding complications. The optimal dose should be adjusted to patient weight by considering the alteration of effective enoxaparin dose with body weight and when needed, it should be calculated by monitoring the antiFXa activity.

References

[1] Freedman K. B., Brookenthal K. R., Fitzgerald R. H. Jr., Williams S., Lonner J. H.: "A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty". *J. Bone Joint Surg. Am.*, 2000, *82-A*, 929.

[2] Lensing A. W., Prins M. H., Davidson B. L., Hirsh J.: "Treatment of deep venous thrombosis with low-molecular-weight heparins. A meta-analysis (see comments)". *Arch. Intern. Med.*, 1995, *155*, 601.

[3] Palmer A. J., Koppenhagen K., Kirchhof B., Weber U., Bergemann R.: "Efficacy and safety of low molecular weight heparin, unfractionated heparin and warfarin for thrombo-embolism prophylaxis in orthopaedic surgery: a meta-analysis of randomised clinical trials". *Haemostasis*, 1997, *27*, 75.

[4] Palmer A. J., Schramm W., Kirchhof B., Bergemann R.: "Low molecular weight heparin and unfractionated heparin for prevention of thrombo-embolism in general surgery: a meta-analysis of randomised clinical trials". *Haemostasis*, 1997, *27*, 65.

[5] Kakkar V. V., Cohen A. T., Edmonson R. A., Phillips M. J., Cooper D. J., Das S. K. *et al.*: "Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group (see comments)". *Lancet*, 1993, *341*, 259.

[6] Kakkar V. V., Boeckl O., Boneu B., Bordenave L., Brehm O. A., Brucke P. *et al.*: "Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism: European multicenter trial". *World J. Surg.*, 1997, *21*, 2, discussion 8.

[7] Nurmohamed M. T., Rosendaal F. R., Buller H. R., Dekker E., Hommes D. W., Vandenbroucke J. P., Briet E.: "Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis". *Lancet*, 1992, *340*, 152.

[8] Samama M., Combe S.: "Prevention of thromboembolic disease in general surgery with enoxaparin (Clexane)". *Acta Chir. Scand. Suppl.*, 1990, *556*, 91.

[9] Gazzaniga G. M., Angelini G., Pastorino G., Santoro E., Lucchini M., Dal Pra M. L.: "Enoxaparin in the prevention of deep venous thrombosis after major surgery: multicentric study. The Italian Study Group". *Int. Surg.*, 1993, *78*, 271.

[10] Haas S., Flosbach C. W.: "Prevention of postoperative thromboembolism with enoxaparin in general surgery: a German multicenter trial". *Semin. Thromb. Hemost.*, 1993, *19*, 164.

[11] Borstad E., Urdal K., Handeland G., Abildgaard U.: "Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery". *Acta Obstet. Gynecol. Scand.*, 1988, *67*, 99.

[12] Borstad E., Urdal K., Handeland G., Abildgaard U.: "Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery, II: Reduced dose of low molecular weight heparin". *Acta Obstet. Gynecol. Scand.*, 1992, *71*, 471.

[13] Prevention of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). *Int. Angiol.*, 1997, *16*, 3.

[14] Dickinson L. D., Miller L. D., Patel C. P., Gupta S. K.: "Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors". *Neurosurgery*, 1998, *43*, 1074.

[15] Stern S. H., Wixson R. L., O'Connor D.: "Evaluation of the safety and efficacy of enoxaparin and warfarin for prevention of deep vein thrombosis after total knee arthroplasty". *J. Arthroplasty*, 2000, *15*, 153.

[16] Shaieb M. D., Watson B. N., Atkinson R. E.: "Bleeding complications with enoxaparin for deep venous thrombosis prophylaxis". *J. Arthroplasty*, 1999, *14*, 432.

[17] Vitoux J. F., Aiach M., Roncato M., Fiessinger J. N.: "Should thromboprophylactic dosage of low molecular weight heparin be adapted to patient's weight? (letter)". *Thromb. Haemost.*, 1988, *59*, 120.

[18] Kirchmaier C. M., Lindhoff-Last E., Rubesam D., Scharrer I., Vigh Z., Mosch G. *et al.*: "Regression of deep vein thrombosis by i.v.-administration of a low molecular weight heparin-results of a pilot study". *Thromb. Res.*, 1994, *73*, 337.

[19] Harenberg J., Huck K., Bratsch H., Stehle G., Dempfle C. E., Mall K. *et al.*: "Therapeutic application of subcutaneous low-molecular-weight heparin in acute venous thrombosis". *Haemostasis*, 1990, *20*, 205.

[20] Harenberg J., Schmidt J. A., Koppenhagen K., Tolle A., Huisman M. V., Buller H. R.: "Fixed-dose, body weight-independent subcutaneous LMW heparin versus adjusted dose unfractionated intravenous heparin in the initial treatment of proximal venous thrombosis. EASTERN Investigators". *Thromb. Haemost.*, 2000, *83*, 652.

[21] Leclerc J. R., Geerts W. H., Desjardins L., Laflamme G. H., L'Esperance B., Demers C. *et al.*: "Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin (see comments)". *Ann. Intern. Med.*, 1996, *124*, 619.

[22] Leclerc J. R., Gent M., Hirsh J., Geerts W. H., Ginsberg J. S.: "The incidence of symptomatic venous thromboembolism during and after prophylaxis with enoxaparin: a multi-institutional cohort study of patients who underwent hip or knee arthroplasty. Canadian Collaborative Group". *Arch. Intern. Med.*, 1998, *158*, 873.

[23] Westrich G. H, Haas S. B., Mosca P., Peterson M.: "Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty". *J. Bone Joint Surg. Br.*, 2000, *82*, 795.

[24] Levine M. N., Planes A., Hirsh J., Goodyear M., Vochelle N., Gent M.: "The relationship between anti-factor Xa level and clinical outcome in patients receiving enoxaparine low molecular weight heparin to prevent deep vein thrombosis after hip replacement". *Thromb. Haemost.*, 1989, *62*, 940.

[25] Bara L., Planes A., Samama M. M.: "Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery". *Br. J. Haematol.*, 1999, *104*, 230.

Address reprint requests to:
A. AYHAN, M.D.
Hacettepe University School of Medicine
Department of Obstetrics & Gynaecology
06100 Sıhhiye, Ankara (Turkey)