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Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of low molecular weight heparin Gynecological ward retrospective analysis

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Abstract

Objectives: To compare the frequency of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing gynecological operations without low molecular weight heparin (LMWH) prophylaxis and those receiving such prophylaxis. *Design*: Retrospective, hospital record-based study. *Material and Methods*: About 1785 consecutive patients without LMWH prophylaxis and 1871 ones treated with nadroparin (Fraxiparine) 7500 ICU s.c. 2 h before the operation and repeated daily for 5–7 days or until the patient was fully mobile. DVT was diagnosed on the basis of clinical symptoms and ultrasound examination, and PE on clinical symptoms, gasometric data, electrocardiography and chest X-ray. *Results*: Among the patients without prophylaxis, four cases of PE occurred (0.22%), two fatal (0.11%), 13 cases of proximal DVT (0.72%) and 41 distal DVT complications (2.3%). In LMWH, group 3 proximal DVT (0.16%) and 18 distal DVT (0.96%) developed but there were no clinically expressed pulmonary embolism. According to the Fisher's exact test, the difference between the complications in the analyzed groups is significant $P < 0.05$. *Conclusion*: The perioperative applying of LMWH to prevent DVT in the patients operated on gynecologically is effective.

Keywords: Deep vein thrombosis prophylaxis; Low molecular weight heparin; Gynecologic surgery

1. Introduction

Deep vein thrombosis (DVT) and its associated sequeles, i.e. pulmonary embolism (PE) and postthrombotic syndrome (PTS) present surgeons with major problems. Gynecological surgery is associated with a medium to high risk of postoperative DVT. Thromboembolic events are frequently clinically occult, and clinical diagnosis is often inaccurate. On objective assessment by radiolabelled fibrinogen leg scanning, 47 (17%) out of 276 patients undergoing gynecological surgery were found to have developed thrombosis [1].

Numerous studies have shown that low molecular weight heparin (LMWH) are at least as effective and safer than unfractionated heparin in the prevention and treatment of venous thromboemboly. This paper presents the gynecological department experience on the LMWH perioperative prophylaxis of DVT.

Compared with unfractionated heparin (UFH), LMWH has a greater ratio of antifactor Xa/antifactor IIa activity [2]. Moreover, the LMWHs have several practical advantages compared to standard heparin, for example almost complete bioavaibility at subcutaneous injection [3], no dose-dependent renal clearance, a more predictable anticoagulant effect at a fixed dose, no need for laboratory monitoring or dose changes [4] and fewer side effects, such as thrombocytopenia [5] or osteoporosis [6].

2. Material and methods

Our work was designed as a retrospective unselected hospital record-based study. About 3656 patients with high or medium risk of DVT operated on in our department between 1988 and 1999 was included in the analysis. The author of the presented paper worked in the department during this period. Perioperative LMWH prevention was gradually applied since the end of 1992. No pharmacological prevention of DVT was applied before. Elastic bandage or elastic compression stockings were worn perioperatively by the patients with highly expressed vein varicosis. The risk of DVT was evaluated according to the table and the list of diseases, states and procedures predisposing to DVT [7]. The 1785 consecutive LMWH not treated patients versus 1871 Fraxiparine recipients were analyzed. The patients were given nadroparin (Fraxiparine) 7500 ICU s.c. (7500 anti-Xa Institut Choay units) 2 h before operation. The fixed

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doses were repeated every 24 h during 5–7 days or to the regaining by the patient sufficient physical activity. The general health state and laboratory data of the patients were examined before operation by internist, anesthesiologist and by other specialists if necessary.

DVT diagnosis was based on clinical signs: pain and swelling of the calf, thigh or the whole leg, fever, tachycardia. The patients suspicious for thrombosis were examined ultrasonographically (USG, Aloka 633 and ATL 800), structurally and by Doppler blood-flow imaging. For the evaluation of the limb veins, the convex and linear 7.5 MHz probes, and to check the pelvic veins the 3.5 MHz probes were applied. The examination was carried out in B-mode (USG-B) in combination with color Doppler technique (USG–CD).

Attention was paid to the shape and echogenicity of the lesions and the reaction of the vessels on the Valsalva's and compression tests. With regard to location, the thrombi clots were divided on the distal (calf veins) and proximal (veins: popliteal, femoral, deep femoral, common, femoral, iliac).

To assess the pulmonary embolism there were respected postmortem examined fatal cases as well as the cured ones with the following clinical symptoms:

1. dyspnea, pleuritic chest pain, cough, tachypnea, tachycardia and apprehension;
2. arterial blood gases — acute respiratory alkalosis, hypocapnia, hypoxemia;
3. electrocardiogram (ECG) — presence of a classic S_1 Q_3 T_3 pattern, with or without a right bundle branch block pattern;
4. chest radiography — a parenchymal infiltrate or pleural reaction and/or effusion.

Hemorrhagic complications were evaluated. Both analyzed groups were compared with respect to number of intraoperative or postoperative transfusions and number of postoperative procedures to control hematomas. For a statistical analysis, the Fischer's exact test was applied.

3. Results

Thrombotic frequency in LMWH-treated patients was significantly diminished in comparison with control ($P < 0.05$, Table 1). Hemorrhage complications rates in

Table 1
Thrombosis events in the analyzed patients ($P < 0.05$)[a]

	Control ($N = 1785$)[b]				LMWH ($N = 1871$)[c]			
	Number of operations	Thrombosis events			Number of operations	Thrombosis events		
		DDVT	PDVT	PE/DPE		DDVT	PDVT	PE/DPE
Abdominal hysterectomy								
Simple	737	20	9	2/1	719	10	1	
m. Wertheim/Meigs								
Cancer of cervix	44	3	1		48			
Stage I-B	39				37			
Stage II-A	5				11			
Debulking in ovarian cancer	26	2			73	2	1	
Stage II	4				11			
Stage III	17				47			
Stage IV	5				15			
Adnexectomy	158	4			180	1		
Vaginal hysterectomy	41	1			40	2		
Colpoperineoplasty with or without conisation or cervical amputation	503	3	2	2	472	2		
Colpocleisis								
m. Neugebauer — Le-Forte	41	2			38			
Vulvectomy								
Radical					5		1	
Carcinoma of the vulva								
Stage II					3			
Stage III					2			
Other operations	228	6	1		326	1		
Total incidence of complications		41	13	4/2		18	3	0/0
Rate (%)		2.3	0.72	0.22/0.11		0.96	0.16	

[a] DDVT: distal deep venous thrombosis; PDVT: proximal deep venous thrombosis; PE: pulmonary embolism, DPE: death due pulmonary embolism.
[b] Age (year) ($x \pm$ S.D.) = 44.8 ± 19.1; body mass index = 24.6 ± 3.0.
[c] Age (year) ($x \pm$ S.D.) = 46.1 ± 19.7; body mass index = 25.2 ± 2.8.

Table 2
Hemorrhage complications rates (%) in the compared groups[a]

Hemorrhage complications rates	Controls ($N = 1785$)	LMWH ($N = 1871$)	Statistical significance
Hemorrhage requiring transfusion number (%)			
Intraoperatively	55/3.1	62/3.3	NS
Postoperatively	43/2.4	49/2.6	NS
Postoperative surgical procedure to control bleeding or evacuate hematomol number (%)			
Intra-abdominal	5/0.28	6/0.32	NS
Tegumental or submucosal	6/0.33	16/0.84	S

[a] NS: statistically not significant; S: statistically significant, $P < 0.05$.

the compared groups did not differ significantly excluding more frequent tegumental hematomas in Fraxiparine recipients (Table 2).

Around 57 (76%) out of all 75 thrombosis incidences in both analyzed cohorts occurred in the patients over 50 year of age. And 78% of events were diagnosed in the calf muscle veins.

In 53 patients (70%), the first symptoms of DVT was noticed between fifth and seventh day after operation, 7 women (9.3%) had to be readmitted after discharge.

In the patients without thrombosis prevention subjected to radical hysterectomy or debulking for ovarian cancer DVT was observed at the rate of 8.5%, to be diminished to 2.3% after Fraxiparine regimen was introduced. In all but one patient afflicted by pulmonary embolism proximal DVT signs proceeded pulmonary symptoms.

In one 30-year-old lean, moderately hypertensioned nulliparous woman distal DVT developed despite of Fraxiparine prophylaxis after ovarian cyst enucleation. She was referred to assess trombophilia, however, further contact with the patient was lost.

It is worth while to mention that sever proximal DVT occurred in a radically vulvectomized 85-year-old patient, 1 month after operation and 1 week after LMWH prevention was ceased.

4. Comment

Contemporary surgery including gynecology is comprehended not only as diagnostico-operative procedures in terms of the method and technique but also as the procedure respecting the prevention of the postoperative complications. From a social point of view, the postoperative complications are less and less acceptable. In the gynecological departments, the majority of patients qualified to operations is burdened with the risk of DVT [1,7]. The analysis of the consecutive 6435 hysterectomies carried out without heparine prevention revealed that the thrombophlebitis after abdominal and vaginal approach occurred in 0.37 and 0.28% of patients whereas PE in 0.37 and 0.28%, respectively, [8]. PE accounted for 5 deaths out of 17 deaths reported in the mentioned review. In another review, DVT after hysterectomy was stated in 0.2% of 1851 women of reproductive age and one of two fatal outcomes was caused by thromboembolic complications [9]. The mentioned above articles reviewing a broad range of adverse effects refer to the period of the 1970s when the problem of DVT was not focused sufficiently and the rate of quoted thrombotic events could be underestimated. It seems a little confusing that the rates of PE and DDVT are similar. Thus, pulmonary embolism, a sever sequeal of vein thrombosis was noticed, whereas it is doubtful if all cases of DVT were diagnosed correctly. A rate 2.4% of DVT after hysterectomies in a large one department analysis seems to be more realistic [10].

During the last two decades the significant advance in DVT prevention has been observed. It results from realizing the problem by the doctors and from the introduction of safer, more effective and convenient alternative for UFH, i.e. LMWHs. The breakthrough in the prevention of DVT came in 1985 when Kakkar demonstrated the superiority of the low molecular weight fraction of heparin for the postoperative prophylaxis of DVT [11]. Whilst the use of UFH has clearly been a major step forward in the prevention of postoperative thrombosis in patients undergoing surgery, LMWHs have two clear advantages: they only need to be administered once daily and they further reduce the risk of thrombosis in general and orthopedic surgery, as shown by the larger trials performed with these agents [11–14]. In gynecological surgery, the benefits of LMWHs on lowering the incidence of DVT is also reported in some papers. However, most of those studies were limited to small cohorts of patients. In 2 patients (1.3%) of 150 patients scheduled for major gynecological surgery developed DVT in the LMWH group. The corresponding figure for heparin was six patients (4.0%). There was no statistically significant difference between the two groups in respect to the bleeding variables such as postoperative drainage, blood transfusions and haematoma [15]. No thromboembolic disease was observed in LMWH-treated 484 women with intermediate risk of thromboembolism who were operated on gynecologically. In seven patients, out of above analyzed wound haematomas was seen [16]. Perioperative LMWH applying (20 and 40 mg Enoxaparin) in the large group of 2339 patients undergoing gynecological surgery completely eliminated DVT and PE incidence. Major intra- or postoperative bleeding was noticed only in 0.3% [17].

Our study confirmed the efficacy of DVT prevention by application of LMWH in the patients operated on gynecologically. In the Fraxiparine recipients, the frequency of

deep thrombose in the calf veins lowered above twice and in the proximal veins above four times in comparison with LMWH not treated patients.

No case of the serious complication of the thrombose, i.e. pulmonary embolism was noticed. Ventilation–perfusion scintigraphy revealed very high probability of silent PE in the patients with proximal and popliteal DVT, reaching ca. 45 and 10%, respectively, [18,19].

Comparing the tendency of thrombosis (17%) after gynecologic surgery evaluated by an improved 125I-fibrinogen uptake test [1] with the rate of clinically manifested complications among the patients of our study (3%) without LMWH prophylaxis one can suppose that about 85% of thrombi formation events remains occult or misdiagnosed.

The tolerability results in terms of intra- and postoperative bleeding, revealed the safety of LMWH. The increased tegumental bleeding incidence in the Fraxiparine group was not of clinical significance and is preferable to the morbidity and mortality risks of thrombosis. Our observations are consistent with the results of the trial based on general surgery [20] and with previously cited papers dealing with gynecological surgery [15–17]. In patients treated with LMWH, perioperatively attention should be paid to meticulous hemostasis, drainage and setonage for minimizing not dangerous but confusing wound hematoma incidences.

Because of the retrospective nature of the data, changes in the imaging instrumentation and the medical staff involved 12 years could bring additional confounders and some bias to the analysis. However, although the data represent a retrospective review of medical records, the development of the technical, medical and mental attitudes allow us to assume that diagnostical piercing to assess thrombosis events enhanced after introducing LMWH. Moreover, the LMWH group contained a greater number of radical oncological operations at the highest risk of DVT than the control.

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