

Prophylaxis of venous thromboembolism in abdominal wall surgery

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Summary: Venous thromboembolic disease (VTD) is a major cause of morbidity and mortality in hospitalized patients, mainly in those undergoing surgery. In this setting, the development of convenient and safe prophylactic measures has become a need. The main role in fulfilling this need is currently played by the so-called low molecular weight heparins (LMWH), among which one of the latest discoveries is bemiparin, a second-generation LMWH. This is a non-randomized, prospective, observational, hospital pharmacovigilance study aimed at assessing the efficacy and tolerability of bemiparin in patients undergoing abdominal wall surgery (eventrations, herniorrhaphies). For this purpose, the study included 203 patients (74% men, 26% women) from 12 Spanish centers with a mean age of 59 years and a moderate to high risk of thromboembolic complications. For subjects with a moderate risk, 2,500 IU were used, and 3,500 IU for high-risk patients, subcutaneously in a single daily dose, starting 2 hours before the procedure and continuing for the risk period or until mobilization of the patient based on medical criteria. Thromboembolic events occurred in only 1.2% of the cases (1 distal DVT and 1 PTE), and no deaths occurred. No treatment-related complications were reported in 78% of the patients, and most complications occurring were not significant: hematoma in the surgical wound, bruising at the injection site... No patient required transfusion of blood derivatives, and no significant differences were seen in laboratory parameters. The absence of treatment-related cases of thrombopenia should be stressed.

Key words: Hernia – Low molecular weight heparin (LMWH) – Thromboembolism prophylaxis

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Venous thromboembolic disease is a major cause of morbidity and mortality in hospitalized patients, causing 100,000 to 200,000 deaths yearly in the United States [Kumar 1993]. In surgical

patients, the risk of VTD is even higher, ranging from 10% to 50% depending on the procedure performed and the presence or absence of other factors [Sama-ma 1999, Caprini 1991]. Therefore, pro-

phylactic measures currently play an essential role in the treatment of surgical patients. An increase in the incidence of deep venous thrombosis (DVT) greater than 50% has been reported in some

series in which no perioperative prophylaxis was given [Ageno 1999].

Since the 1950's, the method most commonly used has been treatment with non-fractionated heparin (NFH), and its prophylactic potential has been recognized in many clinical trials on patients undergoing surgery; in this group, a reduction in the risk of DVT and fatal pulmonary embolism of up to 60-70% has been reported with the administration of subcutaneous NFH [Claggett 1988, Collins 1988] In recent years, a better understanding of the structure of heparins and their mechanism of action has allowed the development of new molecules with a lower molecular weight (low molecular weight heparins, LMWHs), which are the most significant advance in the prophylaxis of venous thromboembolic disease [Kakkar 1982].

Thanks to the lower size of their fragments [Weitz 1997], the antithrombotic activity/hemorrhagic effect ratio is improved compared to NFHs, resulting in a significant advantage with LMWHs in surgical patients. The reduction in the incidence of venous thrombosis when LMWHs are used is approximately 70% [Hirsh 1996], when compared to patients with no prophylaxis. This fact, together with the significant reduction in the risk of bleeding [Hirsh 1996, Leizorovicz 1996], makes them more effective drugs than conventional heparin, as shown in various studies performed in recent years (meta-analysis) [Nurmohamed et al 1992]. On the other hand, the structural differences give these molecules a number of biological and practical advantages over conventional heparin which promote and enhance their use: better absorption from subcutaneous tissue, greater bioavailability (90-98% vs 10%) and lower plasma-protein binding, resulting in a longer half-life (2 to 4 times longer) and allowing administration in single daily doses; and decreased APTT prolongation allowing use with no monitoring controls [Boneu 1994] etc.

The LMWH preparations currently used are obtained with different techniques, have a variable distribution of molecular weights, and show different pharmacokinetic properties. New forms

Table 1. Chemical structure-activity ratio of the hbpm

	MW (daltons)	Anti-Xa	Anti-IIa	
Nandroparin	4,500	90-100	25-30	3:1
Enoxaparin	4,500	100-110	25-30	3-4:1
Dalteparin	5,000	140-160	50-60	2-3:1
Tinzaparin	4,500	90	50	1.5-2.5:1
Bemiparin	3,600	80-110	5-10	8:1

Table 2. Distribution by age, weight and height

	Mean	Median	Standard deviation	Minimum	Maximum
Age	58.67	59.00	13.63	23.00	91.00
Weight	76.17	76	12	31	130
Height	167.40	168	7	150	187

are appearing on the market with lower molecular weights and a better defined composition of their fragments. A greater understanding of structure-activity relationships has led to further modifications in manufacturing process, resulting in a second generation LMWH with a lower mean molecular weight and a more precisely defined composition of polysaccharide chains [Garcia 2000] (Table 1). The LMWH we used has a mean weight ranging from 3,000 to 4,200 daltons (mean value 3,600 daltons), and has been shown to have an antifactor Xa/antifactor IIa ratio of 8:1, which gives the preparation the ability to exert a sustained antithrombotic effect while reducing the risk of bleeding complications. Moreover, its prolonged pharmacokinetic activity allows for administration as single daily doses. To date, it has been shown to be a good agent for antithrombotic prophylaxis of patients undergoing abdominal surgery and hip arthroplasty (clinical trials of Kakkar VV, 1996 and Moreno et al, 1996).

Based on the above results, and to assess the efficacy and tolerability of this second generation LMWH as prophylactic treatment for thromboembolic disease (TED), a non-randomized, prospective, observational, hospital pharmacovigilance study was performed in 203 patients undergoing abdominal wall surgery with a moderate to high risk of suffering this complication, the results of which are reported in this paper.

Material and methods

Patients

A total of 203 patients from 12 Spanish centers undergoing abdominal wall procedures were included for a period of 6 months. The mean age was 59 years (range: 23-91). As regards sex distribution, 73.9% of the patients were men and 26.1% women. (Table 2) All subjects studied had a moderate (81.1% of the total) or high risk (18.9%) of suffering DVT, based on the presence of a number of internationally defined factors (Thromboembolic Risk Factors THRIFT-Consensus Group. BMJ, 1992). Significant factors in our group included: age > 40 years, 181 cases (89.2%); obesity, 80 cases (39.4%); venous insufficiency of the lower limbs, 45 cases (22.2%); trauma or previous surgery, 28 cases (13.8%); heart failure, 9 cases (4.4%); previous DVT or PTE, 7 cases (3.4%); others (AMI, immobilization > 4 days, neoplasm, nephrotic syndrome), 31 cases (15.2%) (Table 3).

The following were excluded from the study: patients with known previous sensitivity to LMWHs; pregnancy, acute bacterial endocarditis; active ulcer disease (gastroduodenal ulcer or ulcerative colitis); known bleeding disorders (thrombophilia, hypo- or dysplasminogenemia, dysfibrinogenemia, fibrinolytic disorders, presence of lupic anticoagulant and/or antiphospholipid antibo-

Table 3. Risk factors of thromboembolic disease in inpatients (Thromboembolic Risk Factors - THRIFT - Consensus Group. BMJ, 1992

Risk factors	No. of cases	% Total
Age > 40 Years	181	89.2%
Obesity Body mass index > 29, or weight 20% above ideal)	80	39.4%
Prominent varicose veins in lower limbs	45	22.2%
Immobilization (bed rest) for 4 days or more	3	1.5%
Treatment with high-dose estrogens (not including oral contraceptives or hormonal replacement therapy)		
History of dvt/pte	7	3.4%
Thrombophilia (deficit of AT III, Prot. C, or Prot. S; Lupic anticoagulant; primary antiphospholipid Sd)		
Trauma or surgery (particularly in pelvis, hip and lower limbs)	28	13.8%
Neoplasm (particularly pelvic, abdominal or with metastases)	5	2.5%
Heart failure	9	4.4%
Recent ami (< 6 months)	4	2.0%
Paralysis of lower limbs	1	0.5%
Sepsis		
Intestinal inflammatory disease		
Nephrotic SD	2	1.0%
Polycythemia		
Paraproteinemia		
Nocturnal paroxysmal hemoglobinuria		
Behcet disease		
Homocystinemia		
Others (Laparoscopy, aortobifemoral bypass, oral antidiabetics...)		
None	16	7.9%
Ninguno	10	4.9%

dies); previous thrombocytopenia associated with heparin, and all patients with a prior platelet count below 100,000/mm³.

The most common surgical procedure (open or laparoscopic surgery) was

unilateral inguinal herniorrhaphy, which was performed in 47.8% of the subjects studied (97 cases), followed by primary eventration (12.3%) and bilateral inguinal herniorrhaphy (11.3%). To a lesser extent, the following were perfor-

med: herniorrhaphies due to recurrence (12.3%), primary or recurrent umbilical herniorrhaphies (10.8%), recurrent incisional hernias (4.4%) and femoral herniorrhaphies (4%) (Table 4).

In 62.9% of the cases, the procedure was performed under epidural anesthesia, while in 32.5% general anesthesia was used. In the remaining 4.6%, local anesthesia associated with sedation was used (Table 5).

Therapy schedule

Each patient received 2,500 IU of LMWH subcutaneously (in a prefilled syringe) if the risk of developing post-surgical TED was moderate, and 3,500 IU if the risk was high, in a single daily dose, starting 2 hours before the procedure.

After the initial dose, 2 hours before surgery, prophylaxis was maintained for an average of 2.52 ± 2 days. In 4.5% of cases, additional preventive measures, such as anti-aggregants (3 cases-1.5%) and other anticoagulants (1%), were also used. In 95.6% of the cases no other drug was used apart from the study drug, but physical measures were used in 24.8% of the patients and maintained for an average of 2.6 days. It must be noted that 15.3% of the patients were treated with non-steroidal antiinflam-

Table 4. Types of hernia

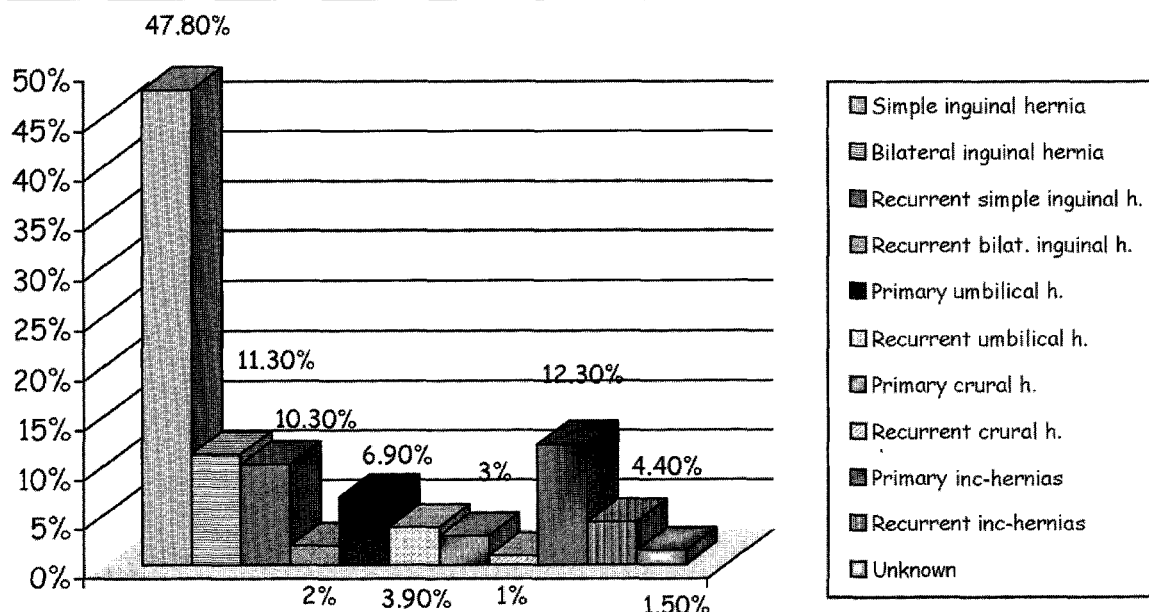
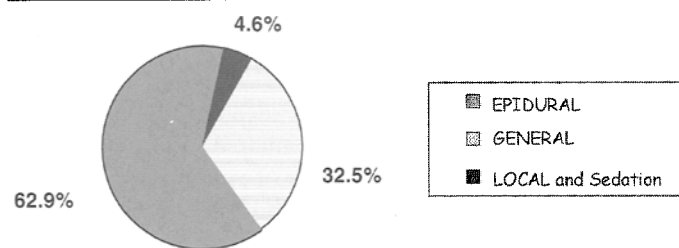


Table 5. Types of anesthesia



matory drugs (NSAIDs) after the surgical procedure.

Study variables

The study objectives were to analyze the tolerability of the LMWH based on the presence of hemorrhagic signs, hematoma at the injection site, skin or systemic allergic reactions and/or thrombopenia; and to record the incidence of deep venous thrombosis and pulmonary thromboembolism in patients undergoing abdominal wall surgery while receiving this preventive therapy with bemparin.

The following assessment criteria were used:

(a) Complications associated with the surgical procedure, including bleeding from the surgical wound, hematoma, and other local side effects;

(b) Major bleeding complications of prophylaxis with heparin, including gastrointestinal bleeding, retroperitoneal hematoma, intraocular bleeding, hemorrhagic stroke, and hematuria;

(c) Skin or systemic allergic reactions;

(d) Thrombopenia;

(e) Hematologic and coagulation tests (INR, APTT, platelets);

(f) Development of DVT and/or pulmonary thromboembolism (PTE) diagnosed by scintigraphy, arteriography or necropsy.

Statistical analysis

For description of the study population, and estimation of adverse events and the pooled cumulative incidence of thromboembolic complications (DVT and PTE), the statistical package SPSS 7.5 was used.

Results

Efficacy analysis

Among the 203 patients included in the study, only two (1.2%) showed post-surgical thromboembolic complications: one distal DVT and one pulmonary embolism. No deaths occurred from this cause.

Safety analysis

77.8% of the patients studied showed no treatment-related complications. In the remaining patients most complications were minor (Table 6), including: intraoperative bleeding complications (4 cases-2%), with a mean loss through drainage of $11.67 \pm 8 \text{ mm}^3$; complications of the surgical wound such as bleeding (3 cases-1.5%) or hematoma (14 cases-6.9%); and local reactions at the injection site such as hematoma (4 cases-2.0%) or bruising (20 cases-9.9%) that were under 2 cm in size in most cases (14 cases-73.7%), and greater than 5 cm in only two patients.

As regards major bleeding complications, these occurred in only two of the subjects analyzed (1.0%), with mean losses through drainage of $154.52 \pm$

Table 6. Complications

Complications	No. of cases
Bleeding during surgery	4
Major bleeding	2
Allergic reactions	0
At the injection site	24
Of the surgical wound	17

76 mm^3 after 48 hours. Nevertheless, these neither threatened life nor required specific treatment like surgery and no transfusion of any blood derivative or other adjuvant drug therapy was required. No hypersensitivity reactions were found in the study population, and no significant changes were seen in laboratory parameters when values prior to admission were compared with discharge values (hematocrit, APTT, INR, platelets). No thrombopenia occurred in association with the use of bemparin (Table 7).

Hospital stay was 3.37 ± 2 days, after which all patients were discharged from the study, including patients with thromboembolic disorders. Specifically, the patient with distal DVT after a 10-day stay in the ward received outpatient prophylaxis with a dose of 3,500 IU over 7 days, while the patient with pulmonary embolism, after a 15-day stay in the ward, was discharged without need of prophylactic treatment.

Follow-up after discharge

Outpatient prophylactic treatment after discharge was continued in 13 of the patients (7.3%) according to medical cri-

Table 7. "Changes in laboratory parameters": admission and discharge values

	Mean	Median	Standard deviation	Minimum	Maximum
Hematocrit (%)					
Admission	42.96	43	4	17	53
Discharge	42.2	5	29	51	
Platelets ($\times 100,000/\text{mm}^3$)					
Admission	219.78	219	47	96	380
Discharge	233.0	233	52	99	332
APTT (seconds)					
Admission	31.82	30	8	9	100
Discharge	35.06	38	8	4	46
INR					
Admission	1.08	1.01	0.26	0.80	2.92
Discharge	1.09	1.07	0.16	0.85	1.57

teria. No serious or severe complications were recorded. Only one patient required readmission, for reasons not related to the thrombotic condition or to disorders associated with bemiparin therapy.

Discussion

In recent years, multiple trials performed to establish the incidence of thromboembolic events in surgical patients and to assess the role of heparin and, more specifically, of the different LMWHs in their prophylaxis have been published. A literature review shows that the majority of these studies reported to date are related to orthopedic surgery (hip arthroplasty, knee prosthesis, etc), or comprise excessively heterogeneous series of patients undergoing abdominal surgery (groups including both abdominal wall surgery and oncological surgery, colorectal surgery, etc).

In this study, we have attempted to use a more specific group of patients in order to obtain results on the occurrence of thromboembolic events only in patients undergoing elective surgery of the abdominal wall and receiving prophylactic treatment with a new second generation LMWH. At this time, there are no trials comparing the efficacy and the safety of bemiparin versus other LMWHs.

In general, some authors have reported an expected incidence of DVT in surgical patients with a low to moderate risk of thromboembolic events of 10%,

and 0-1% for PTE episodes. When different types of LMWHs have been used, decreased incidence rates as low as 6.8% and even 4.7% have been reported, though these data still refer to patients with a low to moderate risk or make no distinction between the different risk groups. In our series, the second generation LMWH studied was able to further improve the results obtained when administered prophylactically in surgical patients undergoing abdominal wall surgery; only one case of DVT (0.5%) and one case of TPE (0.5%) have been found, with no associated mortality, even after administration to patients at moderate or high risk.

A good tolerance of treatment was also found as compared to other series and to the use of NFHs. The number of bleeding complications occurring during the surgical procedure was very low (only 2% of patients, of which only 1% were considered major complications, as compared to 4.7% and even 8.3% in the literature), and no transfusion of blood derivatives was required at any time. No other types of bleeding associated with the use of heparin, such as gastrointestinal bleeding, have been reported, although many of the patients were being treated with NSAIDs, which might have promoted their appearance. There were no instances of retroperitoneal hematoma, intraocular bleeding, hemorrhagic stroke, hematuria, or hematoma related to epidural anesthesia (though this was the procedure used in

62.9% of the cases), as recently reported in some cases of outpatient surgery.

As regards post-operative complications in the surgical wound (bleeding or hematoma), no significant differences were seen compared to those found by other authors. Furthermore, as regards local signs at the injection site, only 2% of the treated patients had a hematoma larger than 5 cm, and in one case treatment had to be discontinued for this reason. The lack of local or systemic hypersensitivity reactions to the LMWH should be stressed.

Finally, it must be stressed that the laboratory parameters obtained during treatment (hematocrit, INR, APTT) showed minimal and not significant changes compared to pre-admission values, particularly in platelet count. No associated episode of thrombopenia was noted, as opposed to an incidence of 2-3.3% in some series treated with NFHs, and a somewhat lower incidence in the case of other LMWHs.

Conclusions

Bemiparin is a second generation LMWH, which can be used safely and effectively for prophylactic treatment of thromboembolic disease in patients undergoing elective abdominal wall surgery having a moderate to high thromboembolic risk. In addition to its convenient administration (a single daily dose), there was a lower rate of bleeding and other complications.

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