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Dabigatran etexilate and LMWH for the prevention of venous thromboembolism in 532 patients undergoing hip surgery

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Abstract. – OBJECTIVE: Patients undergoing total hip replacement (THR) are at high risk of venous thromboembolism (VTE) and according to guidelines they should receive pharmacological prophylaxis. We would like to compare the efficacy, adherence and safety of dabigatran and low molecular weight heparins (LMWH) for the prevention of VTE in patients who underwent THR.

PATIENTS AND METHODS: This study enrolled patients undergoing THR treated with dabigatran (110 mg loading dose then 220 mg/day for 34 days) or the LMWH dalteparin (2500 IU, 6-8 hours before surgery then 5000 IU/day for 35 days). The primary endpoint was adherence to treatment.

RESULTS: Of the 532 patients screened and enrolled in the study, 407 (mean age 57.7 ± 12.3 years) completed the study (211 dabigatran, 196 LMWH). Over the 35 days of treatment, adherence was comparable between dabigatran and LMWH: 10.9% and 14.3% of patients receiving dabigatran and LMWH treatment missed > 1 dose of the drug, respectively. There was a lower need for external support in patients who received dabigatran (8.5% vs 58.2%; $p < 0.0001$) and a lower number of patients receiving dabigatran required support by a professional nurse (1.4% vs 17.3% of patients with LMWH; $p < 0.0001$). Dabigatran and LMWH were similarly well tolerated; however, fewer patients receiving dabigatran reported bleeding events.

CONCLUSIONS: This study demonstrates that dabigatran is associated with high adherence. A lower need for external support in patients who received dabigatran may provide an added benefit compared with other oral treatments for VTE prophylaxis.

Key Words:
Dabigatran; Hip surgery; Low Molecular Weight Heparins; Prevention; Venous thromboembolism.

Introduction

Patients undergoing major orthopaedic surgery, such as total hip or total knee replacement, are considered at high risk of venous thromboembolism (VTE)[1,2,3]. This event may occur during hospital staying or after discharge, with haemodynamic disturbances persisting for at least 2 months after the surgical intervention[2]. In addition, long-term complications such as post-thrombotic syndrome and, more rarely, pulmonary hypertension may develop in some patients with VTE[4,5]. There is, therefore, a clear need for effective strategies to prevent VTE in patients who have undergone major orthopaedic surgery. It has been shown that, in the absence of thromboprophylaxis, the prevalence of venographically confirmed deep vein thrombosis (DVT) ranges from 40 to 60% in the 7-14 days following surgery[2]. Recent guidelines, such as those issues by the National Institute for Health and Clinical Excellence (NICE)[1] and by the American College of Chest Physicians[2] recommend that patients undergoing major orthopaedic surgery should be offered pharmacological prophylaxis, in addition to mechanical prevention methods. Despite these recommendations, thromboprophylaxis is widely underused in clinical practice[6].

Historically, pharmacological agents for the prevention of VTE following orthopaedic surgery included low-molecular-weight heparins (LMWH) such as enoxaparin sodium, fondaparinux sodium, unfractionated heparin and vitamin K antagonist such as warfarin[6]. However, these agents present several limitations which can affect safety, limit patients' compliance and increase the costs for the Healthcare System[6]. These limitations include an increased bleeding risk, the potential for drug-drug interactions, an inconvenient route of administration (continuous intravenous infusion or subcutaneous [SC] injection), and the need of continuous monitoring of coagulation[6,7].

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Newer anticoagulants, such as dabigatran, rivaroxaban and apixaban, are now becoming a part of the pharmacological armamentarium for the prevention of VTE in patients undergoing major orthopaedic surgery[8]. These agents can be administered orally, thus enhancing compliance, and do not require a continuous coagulation monitoring[8]. Among these, dabigatran etexilate (Pradaxa®, Boehringer-Ingelheim) is a prodrug of the direct thrombin inhibitor dabigatran, which is indicated in the EU, and several other countries, for the primary prevention of VTE in adult patients who have undergone elective major orthopaedic surgery[4,9,10]. In the large, randomized, double-blind, phase III, noninferiority trials, RE-MODEL[11], RE-NOVATE[12] and RE-NOVATE II[13], oral dabigatran etexilate 150 or 220 mg once daily, initiated postoperatively was non-inferior to SC enoxaparin sodium 40 mg once daily (initiated prior to surgery) in terms of the incidence of a composite endpoint which included the composite of total VTE events and all-cause mortality. Dabigatran is also associated with an overall favourable benefit-risk profile[5].

However, despite the fact that the efficacy and safety of dabigatran is supported by robust evidence, the conduction of additional studies, conducted in a real-life scenario, has been advocated to better position dabigatran relative to other oral treatment options for VTE prophylaxis[4].

We report here the results of a large, monocentric, observational study which compared dabigatran and low molecular weight heparins (LMWH) for the prevention of VTE in patients who underwent total hip replacement (THR).

Patients and Methods

Study Setting and Design

This monocentric, observational, prospective longitudinal cohort study was conducted at the Rizzoli Institute (Bologna, Italy), one of the Reference Orthopaedic Centres in Italy. The study was initiated in January 2011 and closed in September 2011. The Local Ethical Committee approved the trial protocol, and the study was conducted in accordance to the Helsinki Declaration. Patients signed an informed consent before the inclusion in the trial.

Patients

Patients between 18 and 75 years eligible for THR surgery were eligible for inclusion in this study. Exclusion criteria were: known hypersensitivity to dabigatran etexilate or any excipient; severe renal disease (creatinine clearance < 30 ml/min); hepatic insufficiency or disease; active and clinically-relevant bleeding; any lesion at risk of bleeding; impaired haemostasis of any cause; concomitant treatment with drugs interacting with P-glycoprotein (e.g. verapamil, clarithromycin, quinidine, rifampicin; St John's wort).

Interventions

Patients received dabigatran, at the dosage of 110 mg, according to the following scheme: 1 tablet 1-4 hours after the surgical intervention; 2 tablets/day until day 35 after the intervention. Subjects treated with LMWH (dalteparin 2500 IU, 6-8 hours before the intervention and then 5000 IU/day for 35 days) represented the control group. All patients received mechanical measures for the prophylaxis of VTE, and those assigned to LWMH were monitored for coagulation according to current clinical practice.

There were no restrictions in terms of concomitant treatments. Patients who experienced a VTE were treated according to best clinical practice in centres specialized in the treatment of haemostatic disorders.

Outcomes

The primary outcome was the adherence to treatment, which was assessed using a phone questionnaire. Other outcomes included the number of VTE events, the duration of the hospital stay, the number of patients who started a post-intervention rehabilitation after discharge and the duration of post-intervention rehabilitation and the number of patients who required external support (e.g. by a professional nurse or a family member) after the discharge. Safety was also assessed. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and their potential correlation with study treatments was evaluated by the investigators. The total number and severity of bleeding episodes were also assessed by phone questionnaire.

Statistical Analysis

Statistical analysis was performed with the SAS software, version 17.0 (SAS Incorporation, Chicago, IL, USA). Data were analysed by descriptive statistics. Comparisons between groups were performed, in an explorative fashion, by the

Table I. Patients enrolled in the study.

	Dabigatran	LMWH
Patients enrolled in the study	307	225
Completed the study	211	196
Not completed the study[a]	96	29
Patients excluded from the study[a]	58	4
Reasons for exclusion		
Group change	36	2
No intervention	5	1
Questionnaire not administered	5	0
Questionnaire response not reliable	5	0
Allergy to treatment	1	0
Switch to other drug	2	1
Other reason	1	0
Missing	3	0

[a]Includes patients who were excluded from the study. LMWH, low molecular weight heparin.

chi-Square test, or by student's *t* test, as appropriate. A p-value < 0.05 was considered statistically significant.

Results

Study Population

In total, 532 patients were screened and enrolled in the study. Four hundred and seven patients (211 men; mean age 57.7±12.3 years) completed the study; of these, 211 received dabigatran and 196 LMWH (Table I). The main reasons for exclusion from the study were a change in treatment group (n=38), no intervention received (n=6) and issues with the questionnaire not being administered (n=5) or being unreliable (n=5) [Table I].

Adherence

Twenty-three patients (10.9%) in the dabigatran group did not take all prescribed doses: 20 patients skipped less than 3 doses, and 3 patients skipped an unknown number of doses. The reasons for skipping doses were provided for 5 patients but were not reported for 18 patients. Figures are summarised in Table II. In the LMWH group, 28 patients (14.3%) missed one or more dose of the drug (> 3 doses in one patient and 1-3 doses in all other patients). Missed dose was due to an oversight in all patients; moreover, six patients reported variations from the planned administration schedule after the hospital discharge.

Efficacy Endpoints

During the trial, no patient in the dabigatran group experienced any VTE event, whereas two

Table II. Adherence to treatment, evaluated by telephone questionnaire.

Patients, n	Dabigatran (n = 211)	LMWH (n = 196)	p value[a]
All doses taken	174	166	0.5
Doses skipped			
Any	23	28	0.5
1-3	20	27	
> 3	0	1	
Unknown number	3	0	
Information missing	14	2	
Reasons for skipped dose			
Forgotten	3	0	
Therapy unavailable	2	0	
Other reason	0	0	
No reason provided	18	28	

[a]Assessed using a chi-squared test. LMWH, low molecular weight heparin.

patients in the LMWH group (1%) experienced a VTE event. These included one patient with a reported pulmonary embolism and the other patient experienced a peripheral VTE at the lower limb where the hip replacement was performed.

Patients in the dabigatran and LMWH treatment groups spent a similar amount of time in hospital after hip surgery: the mean duration of in-hospital stay was 6.25 days in the dabigatran group and 6.37 days for patients assigned to LMWH (Table III). One hundred and seven patients (50.7%) in the dabigatran group and 104 (53.1%) of those receiving LMWH were able to complete a post-intervention rehabilitation; the duration of this rehabilitation was 18.69 ± 9.84 days with dabigatran and 18.19 ± 9.40 days in the LMWH patients.

Patients treated with dabigatran had a lower need for external support than those assigned to LMWH (18 [8.5%] vs 114 patients [58.2%]; $p < 0.0001$; Table III). In addition, a lower number of patients in therapy with dabigatran required support by a professional nurse (3 patients; 1.4%), compared with patients receiving LMWH (34 patients; 17.3%; $p < 0.0001$ vs dabigatran).

There were no differences between patients in the dabigatran and LMWH treatment groups with regard to difficulties in following the therapy and laboratory exams needed during the trial period (Table III).

Safety

The safety profiles of dabigatran and LMWH were overall comparable (Table IV). All adverse

Table III. Study efficacy outcomes, assessed by telephone questionnaire.

	Dabigatran (n = 211)	LMWH (n = 196)	p value
Duration of hospital staying, days (mean ± SD)	6.25 ± 2.49	6.37 ± 2.23	0.67[a]
Post-intervention rehabilitation completed, n			
No	102	91	0.7[b]
Yes	107	104	0.7[b]
Duration of post-intervention rehabilitation if completed, days (mean ± SD)	18.69 ± 9.84	18.19 ± 9.40	0.75[a]
Explanation of therapy administration, n			
No	8	6	0.025[b]
Yes	201	189	0.025[b]
Explanation understood	191	180	
Explanation not understood	8	8	
Explanation of therapy administration at home, n			
No	8	6	0.75[b]
Yes	201	189	0.75[b]
Explanation understood	191	180	
Explanation not understood	8	8	
Help needed to complete the therapy administration, n			
No	183	78	< 0.0001[b]
Yes	18	114	< 0.0001[b]
Help provided by			
Family	8	71	
Nurse	2	30	< 0.0001[b]
Care organization	4	4	
Other caregiver	1	5	
Family + nurse	1	4	
Difficulties in following the therapy, n			
No	200	188	0.6[b]
Yes	4	6	0.6[b]
Reasons for difficulties			
Other pathology interfering	1	0	
The patient did not like the administration method	0	3	
Drug not available	0	2	
Help not found to complete the administration	0	1	
Laboratory exams needed, n			
No	74	72	0.75
Yes	127	116	0.75

[a]Assessed using a *t*-test. [b]Assessed using a chi-squared test. LMWH, low molecular weight heparin; SD, standard deviation.

Table IV. Adverse events in the safety analysis set.

Adverse events, n	Dabigatran (n = 211)	LMWH (n = 196)	p value[a]
Any	44	31	0.2
Nausea	8	0	0.015
Epigastric pain/dyspepsia	7	1	0.07
Haematoma	1	17	< 0.0001
Itch	5	1	
Anaemia	3	0	
Dryness	2	0	
Bleeding	4	0	
Burning sensation	2	2	
Cold limbs	2	1	
Body odour	2	0	
Swelling	0	2	
Redness	0	1	
Olfaction problems	1	0	
Fever	1	0	
Headache	1	0	
Irritability	1	1	
Diarrhoea	1	0	
Constipation	1	0	
Increased urination	1	0	
Pain	0	1	
Decreased platelets	0	1	

[a]Assessed using a chi-squared test. LMWH, low molecular weight heparin.

events were mild or moderate and were successfully managed with standard medical treatment. The most frequent adverse event in patients treated with dabigatran was epigastric pain/dyspepsia (7 patients; 3.3%) and nausea (8 patients; 3.8%); however, none of them discontinued therapy. In contrast, in the LMWH group, the most frequent adverse event was the development of haematomas (17 patients; 8.7%), which was reported in significantly more patients in the LMWH group ($p < 0.0001$). No clinically-relevant alterations in the laboratory parameters were reported in either group. Four patients (1.9%) experienced difficulties in taking dabigatran therapy, versus 6 (3.1%) subjects assigned to LMWH ($p = 0.6$). All bleeding events were of mild severity and fewer patients receiving dabigatran reported bleeding events at the phone questionnaire (19 vs 50 patients).

Discussion

This study investigated patient adherence and the need for further support in patients receiving VTE prophylaxis with dabigatran or LMWH who have undergone THR. We found that treatment adherence was comparable between dabigatran and LMWH recipients. However, there was a lower need for external support in patients who received dabigatran. In particular, fewer patients receiving dabigatran required support by a professional nurse or an explanation of how to administer their treatment compared with patients receiving LMWH.

Approximately 80% of patients receiving dabigatran or LMWH adhered to treatment in this study. To date and at the best of our knowledge, no other studies investigating the adherence of patients to dabigatran therapy following THR have been conducted; however, one study has investigated patient compliance to 35-40 days of thromboprophylaxis with dabigatran following THR[14]. Our study showed an overall compliance of 98.1% to dabigatran in this patient population which is higher than the adherence seen in this study[14]. While adherence and compliance are two separate endpoints (adherence is the act of filling or refilling new prescriptions and compliance is the act of taking medication as prescribed or on schedule), it is expected that they would be somewhat similar in this patient population. However, we speculate that the observed difference may be due to improved patient educa-

tion on their medication following surgery by their health care professionals. Nevertheless, an adherence of ~80% is still considered high considering that the consumption of dabigatran was in most cases without the supervision of a medical care professional and shows that patients receiving dabigatran could have improved outcomes due to receiving greater amount of the drug.

To our knowledge, this is the first study that investigates the requirement of external support in patients who have undergone THR and are receiving dabigatran for VTE prophylaxis. This study indicates that the lower need for external support shown in patients who received dabigatran, compared with LMWH, may provide an added benefit compared with other oral treatments for VTE prophylaxis. Further studies investigating this relationship are warranted.

The results of this study add to the evidence supporting the efficacy and safety of dabigatran, particularly the results of the RE-NOVATE[12] and RE-NOVATE II[13] studies which showed that dabigatran was as effective as enoxaparin at reducing the risk of VTE and after THR surgery and that dabigatran is generally well tolerated. Based on the results of the RE-NOVATE and RE-NOVATE II studies, NICE have surmised that dabigatran is very likely to be of equivalent clinical and cost effectiveness to enoxaparin or fondaparinux in the prevention of VTE. As such, they acknowledge that oral administration of dabigatran, which has no need for patient monitoring, may reduce administration costs and support adherence to treatment, making dabigatran a valuable alternative to enoxaparin or fondaparinux[15].

This monocentric study is lacking of robust baseline data. Further, the adherence to the treatment and occurrence of bleeding events was assessed by phone questionnaire and was consequently hard to verify.

Conclusions

This study supports the efficacy and safety of dabigatran and demonstrates the high adherence associated with this drug. A lower need for external support in patients who received dabigatran may provide an added benefit compared with other oral treatments for VTE prophylaxis. Further investigations are warranted.

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Conflict of Interest

Stefano Bonarelli received honoraria as speaker for courses from Boehringer-Ingelheim, Italy. The other authors declare no conflict of interest.

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