

# A prospective observational study on the effectiveness and safety of bemiparin, first dose administered 6 h after knee or hip replacement surgery

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## Abstract

**Introduction** Bemiparin has shown to be effective and safe in clinical trials in total knee or hip replacement.

**Materials and methods** We conducted a prospective, open, multicentre, uncontrolled study to audit the utilisation patterns of bemiparin 3,500 IU/day, first dose administered 6 h after surgery, in 1,009 patients undergoing total hip or knee replacement surgery in standard clinical practice. We analysed rates of documented symptomatic venous thromboembolism (VTE) [deep-vein thrombosis (DVT) and pulmonary embolism (PE)] confirmed by objective methods, major bleeding, death, thrombocytopenia and other adverse events up to 6 weeks.

**Results** Rate of documented symptomatic DVT was 0.3% (95% CI, 0.1–0.9%). No cases of documented PE were reported. There were 14 (1.4%) major bleedings (95% CI, 0.8–2.3%). Neuraxial anaesthesia was used in 937 (92.9%) patients. There were no cases of spinal haematoma, fatal bleeding or bleeding in critical organs. There were 6 (0.6%) cases of mild thrombocytopenia,

which did not require treatment discontinuation. No cases of severe type II heparin-induced thrombocytopenia were observed. There were no deaths during bemiparin prophylaxis. The median length of hospitalisation was 9 days and 92.5% of patients continued prophylaxis post-hospitalisation for a total median time of 38 days. There were no thromboembolic or bleeding complications during post-hospitalisation prophylaxis. Postoperative start of prophylaxis with bemiparin permitted that 29.3% of patients could be admitted to hospital the same day of the intervention.

**Conclusion** Bemiparin prophylaxis, started 6 h after surgery and given for 5–6 weeks after total hip or knee replacement, was associated with low rates of VTE, major bleeding and other adverse events in normal clinical practice. Bemiparin thromboprophylaxis started 6 h after surgery makes neuraxial anaesthesia/analgesia procedures easier, without compromising efficacy.

**Keywords** Bemiparin · Heparin · Knee replacement · Hip replacement · Thromboprophylaxis · Venous thromboembolism · Deep-vein thrombosis · Pulmonary embolism

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## Introduction

Patients undergoing major orthopaedic surgery, such as total knee replacement (TKR) or total hip replacement (THR) surgery, represent a group at particularly high risk of venous thromboembolism (VTE) [9, 15]. The risk remains high for several weeks after surgery [9]. In these patients, routine chemical thromboprophylaxis has been the standard of care for the past

20 years, thus reducing overall mortality and fatal pulmonary embolism (PE) [5]. Low-molecular-weight heparin (LMWH) is significantly better than warfarin or aspirin in preventing deep-vein thrombosis (DVT) after major orthopaedic surgery [23]. Mechanical means of prophylaxis could provide an additional efficacy [9, 19]. The benefits of neuraxial anaesthesia (i.e. spinal or epidural) are also well established [1, 18].

The widespread use of thromboprophylaxis and neuraxial anaesthesia in patients undergoing major orthopaedic surgery—these procedures are used in 60–95% of all THR or TKR surgeries [8, 14]—makes it necessary to develop new strategies to enhance safety in these patients. Neuraxial anaesthesia should generally be avoided in patients whose preoperative haemostasis is impaired by antithrombotic drugs [9], because of the increased risk of spinal haematoma [11, 21]. In order to avoid preoperative impaired haemostasis, thus minimising the risk of spinal haematoma and intraoperative bleeding, it would be reasonable to start prophylaxis several hours after surgery, whenever the efficacy of LMWH should not be compromised [20, 24].

Bemiparin is a new second-generation LMWH [16] that has shown greater efficacy than standard heparin in a comparative clinical trial conducted by Kakkar et al. in the prevention of VTE after THR surgery [12]. Bemiparin may be started before or after surgery, whereas recommendations for other LMWHs in Europe primarily involve preoperative initiation [4].

In a recent, comparative clinical trial with enoxaparin in total TKR, bemiparin 3,500 IU/day started 6 h after surgery showed a non-significant trend towards a lower incidence of documented symptomatic VTE as compared with enoxaparin 4,000 IU/day started 12 h before surgery, with a similar safety profile [14].

This observational study was designed to gain additional clinical experience with postoperative start of bemiparin prophylaxis in a large population of orthopaedic patients in normal clinical practice.

## Materials and methods

This study was designed as a prospective, uncontrolled, open-label, multicentre, observational “real life” assessment of bemiparin, started 6 h after surgery, in patients undergoing TKR or THR surgery. The study was conducted according to the Spanish requirements for observational studies (Circular 4/2000 of the Spanish Medicines Agency) and European Guidelines (CPMP/PhVWP/109/99/corr).

Any patient undergoing TKR or THR surgery was eligible for inclusion in the study. There were no pre-established exclusion criteria in the protocol.

All patients received once daily subcutaneous injections of bemiparin 3,500 IU, starting 6 h after surgery, that were administered during the risk period according to the physician’s criteria. The extent of exposure was shown by the median days (first and third quartile) of bemiparin prophylaxis. Non-pharmacological treatments, such as active or passive mobilisation, elastic bandages and/or intermittent pneumatic compression devices, were used according to the usual practice at each centre and were recorded in the case report form.

The primary effectiveness outcome was documented symptomatic VTE, including DVT, PE or both. If VTE was clinically suspected, it had to be confirmed by objective methods (i.e. Doppler ultrasound or ascending contrast venography for DVT, high-probability lung scanning, pulmonary angiography, helical computed tomography for non-fatal PE, or necropsy in cases of suspected fatal PE). The decision whether or not to perform confirmatory tests was left to physicians’ criteria.

The primary safety endpoint was the occurrence of major bleeding, defined as clinically overt bleeding associated with fall in haemoglobin of at least 2 g/dl or requirement of a transfusion of 2 or more units of blood, bleeding in critical organs (intracranial, spinal, retroperitoneal or intraocular bleeding), fatal bleeding, bleeding requiring reoperation to control bleed, or any bleeding requiring treatment cessation. Minor bleeding was any other overt bleeding that did not fulfil the criteria of major bleeding.

The following analytical parameters were tested: haematocrit, hemoglobin, platelets, AST (aspartate aminotransferase), ALT (alanine aminotransferase) and GGT (gamma-glutamyl transpeptidase). Thrombocytopenia was defined as a platelet count < 150,000/mm<sup>3</sup> during bemiparin prophylaxis. Postoperative anaemia was defined as a haemoglobin value < 12 g/dl at hospital discharge. The incidence of death, allergic reactions, wound haematoma/bruising and reactions at injection site were also assessed.

Three visits were scheduled: the first one the day of surgery (baseline), the second one at the time of hospital discharge (outcome assessment visit), and the third one during the first outpatient visit (follow-up visit), according to standard clinical practice.

Ninety-five percent confidence intervals were calculated for the rates of VTE, major and minor bleeding events, thrombocytopenia, deaths and allergic reactions. These calculations were performed using SPSS software, version 7.5.

**Table 1** Demographic data and other characteristics

Characteristic	Knee replacement, <i>N</i> = 653	Hip replacement, <i>N</i> = 356	Total patients, <i>N</i> = 1,009	<i>N</i> assessable
<b>Demographic data</b>				
Age, mean (SD)	71.6 (6.8)	69.4 (11.7)	70.9 (8.5)	547
Sex, <i>n</i> (%)				1,007
Male	177 (27.1)	157 (44.3)	334 (33.2)	
Female	476 (72.9)	197 (55.7)	673 (66.8)	
Weight (kg), mean (SD)	76.7 (10.9)	77.5 (11.9)	76.9 (11.2)	928
Height (cm), mean (SD)	162.3 (8.7)	165.9 (8.5)	163.4 (8.8)	898
BMI, kg/m <sup>2</sup> , mean (SD)	29.2 (4.7)	28.2 (3.8)	28.9 (4.1)	898
Admission on the same day of surgery, <i>n</i> (%)	167 (29.5)	74 (28.9)	241 (29.3)	822
Hospitalisation days, median (first, third quartiles)	9.0 (8, 12)	9.0 (8, 12)	9.0 (8, 12)	867
<b>Surgery information</b>				
Type of surgery, <i>n</i> (%)				945
Primary joint replacement	595 (96.7)	297 (90)	892 (94.4)	
Revision surgery	20 (3.3)	33 (10.0)	53 (5.6)	
Type of prosthesis, <i>n</i> (%)				968
Cemented prosthesis	530 (83.9)	90 (26.8)	620 (64.1)	
Uncemented prosthesis	102 (16.1)	246 (73.2)	348 (35.9)	
Type of anaesthesia used, <i>n</i> (%)				1,009
Neuraxial	589 (90.2)	293 (82.3)	882 (87.4)	
Spinal	351 (53.8)	205 (57.6)	556 (55.1)	
Epidural	238 (36.4)	88 (24.7)	326 (32.3)	
Combined neuraxial–general	35 (5.4)	20 (5.6)	55 (5.5)	
General	29 (4.4)	43 (12.1)	72 (7.1)	
Operative transfusions, <i>n</i> (%)				980
Autologous	80 (12.2)	26 (7.3)	106 (10.8)	
Heterologous	89 (13.6)	69 (19.4)	158 (16.1)	
Both	5 (0.8)	2 (0.6)	7 (0.7)	
Tourniquet and/or careful haemostasis previous to wound closure, <i>n</i> (%)	521 (82.1)	152 (52.1)	673 (72.6)	927
Surgery duration, minutes, mean (SD)	92.0 (33.4)	103.3 (29.0)	95.7 (32.4)	783
<b>Postoperative period</b>				
Time to ambulation, days, mean (SD)	3.65 (2.37)	4.34 (3.20)	3.87 (2.68)	917
Elastic graduated pressure stockings, <i>n</i> (%)	218 (37.6)	43 (14.5)	261 (29.8)	876
Intermittent pneumatic compression, <i>n</i> (%)	45 (7.8)	1 (0.3)	46 (5.3)	876
Patient exposure to bemiparin 3,500 IU				922
In-hospital doses, median (first, third quartiles)	8 (7, 10)	8 (6, 10)	8 (6, 10)	
Out-hospital doses, median (first, third quartiles)	30 (26, 36)	30 (26, 34)	30 (26, 36)	
Extended prophylaxis out-hospital, <i>n</i> (%)	589 (90.5)	342 (96.3)	931 (92.5)	1,006
Observation period, median (first, third quartiles)	39 (32, 43)	39 (31, 42)	39 (32, 43)	843

Mean, median and percents are calculated for assessable patients

*BMI* body mass index

## Results

Between November 2001 and March 2003, 1,009 patients were enrolled in 23 Spanish centres. Baseline characteristics of patients included in the study are shown in Table 1. Among the 1,009 patients included, 653 (64.7%) underwent TKR surgery and 356 (35.3%) underwent THR surgery. Mean age of patients included was 70.9 years. Most patients were females (66.8%), and mean body weight was 76.9 kg. Neuraxial

anaesthesia, alone [882 patients (87.4%)] or in combination with general anaesthesia [55 patients (5.5%)], was administered to 937 (92.9%) patients. Patients received bemiparin prophylaxis for a median time of 8 days during hospitalisation. More than 90% of patients continued extended outpatient prophylaxis with bemiparin 3,500 IU/day for 30 additional days (median) (Table 1). Twenty-nine percent of patients were admitted to hospital on the same day of surgery (Table 1).

**Table 2** Overall effectiveness and safety during prophylaxis period

Variable	Knee replacement N = 653 [% (n)]	Hip replacement N = 356 [% (n)]	Total Bemiparin N = 1,009 [% (n)]	95% CI (%)
Documented symptomatic VTE	0.3 (2)	0.3 (1)	0.3 (3)	0.1–0.9
Proximal DVT	0.3 (2)	0 (0)	0.2 (2)	0.0–0.7
Distal DVT	0 (0)	0.3 (1)	0.1 (1)	0.0–0.6
Non-fatal PE	0 (0)	0 (0)	0 (0)	0.0–0.4
Fatal PE	0 (0)	0 (0)	0 (0)	0.0–0.4
Major bleeding	0.8 (5)	2.5 (9)	1.4 (14)	0.8–2.3
Minor bleeding	7.5 (49)	9.0 (32)	8.0 (81)	6.4–9.9
Death by any cause	0 (0)	0 (0)	0 (0)	0.0–0.4
Thrombocytopaenia	0.5 (3)	0.8 (3)	0.6 (6)	0.2–1.3

VTE venous thromboembolism, DVT deep-vein thrombosis, PE pulmonary embolism

All patients had an outcome assessment at hospital discharge. Three (0.3%; 95% CI, 0.1–0.9%) of the 1,009 patients experienced symptoms of DVT (Table 2). All of them occurred while in the hospital, 6–9 days after surgery. The events were two proximal DVTs after TKR and one distal DVT after THR, which were confirmed by Doppler ultrasound. One patient undergoing KR developed symptoms of PE on post-operative day 4. However, the event was ruled out by lung scanning. There were no cases of VTE after hospital discharge.

Major bleeding occurred in 14 (1.4%; 95% CI, 0.8–2.3%) of the 1,009 patients (Table 2). All major bleeding events occurred during hospitalisation, and included ten cases of excessive wound bleeding, three haemarthroses of the prosthetic joint, and one gastrointestinal bleeding (coffee ground vomiting). None were fatal. Of all major bleedings, one excessive wound bleeding occurred before the first bemiparin dose, and required reoperation for control. The major gastrointestinal bleeding occurred in one patient with a clinical history of grade III gastroesophageal reflux and hiatal hernia who was concomitantly receiving an intravenous non-steroidal anti-inflammatory drug (NSAID). Both medications, NSAID and bemiparin, were stopped. Two days after patient recovery, bemiparin was re-started and the adverse event did not recur. A total of 937 (92.9%) patients received neuraxial anaesthesia, and no cases of spinal haematoma were reported.

There were no deaths during the treatment period with bemiparin. Thrombocytopaenia was seen in 6 (0.6%; 95% CI, 0.2–1.3%) of the 1,009 patients included (Table 2). Thrombocytopaenia ranged from 80,000/mm<sup>3</sup> to 135,000/mm<sup>3</sup>, and none of this required treatment discontinuation. There were no cases of severe heparin-induced thrombocytopaenia (HIT type-II). Mild to moderate postoperative anaemia (Hb 8–12 g/dl) was shown in 484 (48.0%) patients. Only three (0.3%) patients had haemoglobin levels <8 g/dl during

the study. Mild, transient increases in serum aminotransferases, always less than three times the upper normal limit, were reported in 2.1% (AST), 4.0% (ALT) and 3.2% (GGT) of patients included. None of the cases were clinically significant and none of them required treatment discontinuation. A minor allergic reaction, consisting of mild urticaria around the injection site, was seen in one patient (0.1%; 95% CI, 0.0–0.6%). Treatment was not discontinued. There were no cases of systemic or general allergic reactions. Among all patients included, 16.1% developed surgical wound haematoma/bruising (95% CI, 13.8–18.5%), and none of them needed local reintervention or prolonged hospitalisation. Overall, 1.5% patients experienced surgical wound infection. Only 6 of 23 centres reported any surgical wound infection. Injection site reactions were reported in 20% of patients. Most of these reactions were mild ecchymoses. There were no cases of injection site haematomas greater than 5 cm in diameter or requiring treatment discontinuation. There were no rare or unexpected adverse drug reactions to bemiparin during the study.

#### Follow-up

A total of 931 patients (92.5%) received extended outpatient prophylaxis. There were no thromboembolic or haemorrhagic complications during the time from hospital discharge to the follow-up visit. A 72-year-old male patient with clinical history of ischaemic heart disease died from an acute myocardial infarction 2 months after TKR surgery and 20 days after the last bemiparin dose.

#### Discussion

A low incidence of documented symptomatic VTE was seen when bemiparin was started 6 h after surgery in

normal clinical practice. The incidence of documented symptomatic VTE during hospitalisation in our observational study was 0.3% (two proximal DVTs, one distal DVT, and no cases of documented symptomatic PE), which is entirely comparable and even lower than the incidence of symptomatic VTE reported with other antithrombotic drugs during short-term prophylaxis after major orthopaedic surgery [22]. It must be pointed out that comparisons of the results of observational studies with those of clinical trials should be interpreted with caution, given the methodological differences between the two types of studies.

In our study, more than 90% of patients received extended prophylaxis with bemiparin for a median time of 38 days. No cases of VTE were reported during extended bemiparin prophylaxis after hospital discharge. The incidence is lower than the 1.3% (range 0–3.5%) rate of symptomatic VTE reported in a recent meta-analysis with other LMWH during extended prophylaxis after TKR or THR [6], or the 3.3% incidence with placebo in the same meta-analysis [6], and lower than the 0.3% incidence of symptomatic VTE during extended prophylaxis with fondaparinux [7]. The duration of prophylaxis used in our study is consistent with current recommendations [9] including the use of prolonged prophylaxis for up to 4–5 weeks in patients undergoing THR surgery. The need of prolonged thromboprophylaxis after TKR is still in debate [9]. Nevertheless, a recent meta-analysis showed that, among patients undergoing THR or TKR, extended-duration prophylaxis significantly reduced the frequency of symptomatic venous thromboembolism [6]. The reduction in risk of symptomatic VTE was higher in THR than in TKR [6].

We found a low incidence of major bleeding complications—1.4%—which agrees with the reported incidence for short-term in-hospital prophylaxis with bemiparin during clinical trials in major orthopaedic surgery [12, 14]. This rate is lower than the 2.7% incidence reported with fondaparinux and similar to the 1.7% incidence reported with enoxaparin during short-term in-hospital prophylaxis after major orthopaedic surgery in selected populations from clinical trials [3]. In addition, no major bleeding complications were reported during extended outpatient prophylaxis with bemiparin in our study, which is similar to the 0.1% incidence of major bleeding found in a recent meta-analysis of extended LMWH prophylaxis in TKR or THR surgery [6], and lower than the 2.4% incidence seen during extended outpatient prophylaxis with fondaparinux [7].

In our observational study, there were no deaths during the study period. All cases of thrombocytopenia were mild to moderate and did not require treatment discontinuation. There were no cases of type-II severe

thrombocytopenia. The rates of surgical wound haematoma/bruising and injection site reactions were similar to those previously reported with bemiparin, and lower than reported with enoxaparin in a comparative clinical trial in TKR [14]. No rare or unexpected adverse drug reactions to bemiparin occurred during the study.

In our study, nearly one-third of patients included were admitted to hospital the same day of surgery, instead of on the evening before the procedure, thus potentially reducing hospital stay costs. In a recent pharmaco-economic study, bemiparin administered postoperatively was a dominant strategy over enoxaparin administered preoperatively, offering better outcome at lower cost [10].

In our study, neuraxial anaesthesia was used alone or combined with general anaesthesia in more than 90% of patients, and no cases of spinal haematoma were reported. Although the timing of the first administration of thromboprophylaxis is controversial [17], it is recognised that bemiparin administration started 6 h after surgery does not compromise efficacy [14], and is compatible with neuraxial anaesthesia techniques [11]. On the contrary, patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, needle placement should occur at least 10–12 h after the LMWH dose [11]. Thromboprophylaxis started less than 6 h after surgery may increase the risk of bleeding without improved efficacy [17]. Initiation 12–24 h postoperatively may be less effective than initiation at 6 h [17].

This study has several methodological limitations. However, the results of this observational study should be interpreted in the setting of normal clinical practice. This type of studies add information that is not available in randomised controlled trials [2] where exclusion criteria, limited sample size and use in specific clinical situation leads to significant loss of useful pragmatic data. Therefore, we were able to assess the “real life” effect of bemiparin in a large audit of orthopaedic patients. Clinical endpoints are of major value to assess the effects of a new drug in clinical studies on the prevention of VTE [13].

In conclusion, bemiparin prophylaxis, started 6 h after surgery and given for 5–6 weeks after THR or TKR was associated with low rates of VTE, major bleeding and other adverse events in normal clinical practice. Moreover, bemiparin thromboprophylaxis started 6 h after surgery minimises the risk of spinal haematoma and makes neuraxial anaesthesia/analgesia procedures easier, without compromising efficacy.

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## Appendix

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