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ORIGINAL ARTICLE

Prospective study on the efficacies of fondaparinux and enoxaparin in preventing venous thromboembolism after hip fracture surgery

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Abstract
Background Venous thromboembolism (VTE) is a common complication in hip fracture surgery (HFS). Fondaparinux (FPX) and enoxaparin (ENO) have been reported to decrease the incidence of VTE after HFS. The purpose of this study was to determine the efficacies of FPX and ENO and the superior agent for preventing VTE after HFS by performing a prospective study in a Japanese population.
Methods Eighty-four Japanese patients who underwent HFS were assigned to either FPX (received FPX 1.5 or 2.5 mg/day for 14 days), ENO (received ENO 2000 IU once or twice/day for 14 days), or untreated control (CTRL) groups in order of surgery. All patients underwent ultrasonography of the lower extremities 7 days after HFS to evaluate the extent of deep-vein thrombosis. Incidence of VTE, D-dimer values measured at admission and 7 and 14 days after HFS, and the side effects of FPX and ENO were compared.
Results The incidence of VTE and the D-dimer values on days 7 and 14 in the FPX group were significantly lower than the corresponding levels in the CTRL group ($P < 0.05$). The D-dimer values on day 7 in the ENO group were significantly lower than those in the CTRL group, whereas the incidence of VTE was not significantly different. Side effects were observed in 3 cases: major bleeding occurred in 2 patients who received FPX, whereas minor bleeding occurred in 1 patient who received ENO.
Conclusions We concluded that FPX was the superior agent for preventing VTE after HFS. However, patients receiving FPX should be monitored for bleeding.

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Introduction

Hip fracture is a common injury in elderly people, with many complications occurring perioperatively. Venous thromboembolism (VTE) is one such complication that occurs after hip fracture surgery (HFS), total hip arthroplasty (THA), and total knee arthroplasty (TKA) [1–7]. In the absence of prophylaxis, the incidence of fatal pulmonary embolism (PE) after HFS has been reported to be 0.4–7.5% [1].

Preventive anticoagulant therapy is increasingly being used as a countermeasure for this complication. Fondaparinux sodium (FPX) and enoxaparin sodium (ENO) were approved for use in therapy for VTE by the Japanese Ministry of Health, Labor and Welfare in 2007 and 2008, respectively. Eriksson et al. [2] reported that the incidence of VTE after treatment with FPX (8.3%) was significantly lower than that after treatment with ENO (19.1%) in a randomized controlled trial (the PENTHIFRA study). In 2 separate studies in Japan, Fuji and Fujita reported that the incidences of VTE after HFS in patients treated with FPX and ENO were 21.6% [7] and 14.0% [8], respectively. However, the incidences of VTE in those studies were different from those seen in the PENTHIFRA study [2], which can be attributed to the differences in patient backgrounds in

these 2 nonrandomized studies [7, 8]. We have previously reported the efficacy of FPX in preventing VTE after HFS in a Japanese population in a randomized controlled trial [9]. However, no study has directly compared the efficacies of FPX and ENO in preventing VTE in Japanese populations.

The purpose of the present study is therefore to answer the question: which is the superior and safest agent for preventing VTE after HFS in Japanese populations? We evaluated the incidence of VTE after HFS in Japanese subjects who received FPX or ENO by performing a prospective study. In addition, D-dimer values—useful markers for VTE [9–11]—and side effects involving bleeding (i.e., major or minor bleeding) were investigated.

Patients and methods

Patients

A total of 102 consecutive patients who underwent HFS at the institution of the first author between December 2008 and March 2010 were enrolled in this study. Written informed consent was obtained from all patients. The study protocol was approved by the ethics committee of the first author's institution.

Exclusion criteria

The exclusion criteria for this study, in addition to the patient disagreeing with the study protocol, were a preoperative creatinine clearance (Ccr) rate of <30 ml/min measured using the Cockcroft–Gault formula [12], a serious general condition (i.e., heart failure or multiple injury), or the occurrence of VTE before the administration of drug therapy. The details of the 18 patients who were excluded from this study are presented in Table 1. One patient in the FPX group who did not receive medication on one occasion during the administration period was excluded from the data analysis.

Study design

The 84 eligible patients were allocated to untreated control (CTRL) ($n = 29$), FPX ($n = 27$), or ENO groups ($n = 28$) in order of surgery, i.e., the first eligible patient was classified into the CTRL group, the next patient to the FPX group, the third patient to the ENO group, and so on.

Table 1 Exclusion criteria

Criterion	Number of subjects
Consent not provided	4
Preoperative creatinine clearance <30 ml/min	8
Occurrence of VTE before drug administration	2
Serious general condition	3
Lack of fondaparinux administration	1

VTE venous thromboembolism

Intervention

Patients assigned to the FPX group received FPX 1.5 or 2.5 mg/day in the form of a subcutaneous injection (Arixtra; GlaxoSmithKline, Tokyo, Japan) for 14 days, starting the day after the surgery (at least 24 h after surgery). The ENO group patients subcutaneously received 2000 IU of ENO once or twice per day (Crexine; Sanofi-aventis, Tokyo, Japan) for 14 days starting the day after the surgery (at least 24 h after surgery). The administration dose in these 2 groups was determined on the basis of the Ccr rate calculated using the Cockcroft–Gault formula [12]. Patients with Ccr >50 ml/min received FPX 2.5 mg/day or 2000 IU of ENO twice per day. In patients with Ccr 30–50 ml/min, the administration doses depended on age or body weight; namely, patients aged >85 years or whose body weight <40 kg received FPX 1.5 mg/day or 2000 IU of ENO once per day. These administration doses followed drug information released in Japan. If epidural catheterization was introduced at surgery, the catheter was to be removed at least ≥2 h before the first administration of FPX or ENO. The administration of the drugs was discontinued in patients who exhibited any side effects. All patients in this study were encouraged to move both ankles immediately after awakening from anesthesia, and to get out of bed after the drainage tube was removed. Compression stockings (T.E.D. anti-embolism stockings; TYCO Healthcare, Mansfield, MA, USA) and foot pumps (AV Impulse; Kobayashi Medical, Osaka, Japan) were used as mechanical prophylaxis in all patients from the day of admission to day 7 after surgery.

Assessment of endpoints

Ultrasonography (US: Prosound ALPHA 10, linear probe; ALOKA, Tokyo, Japan) was performed in all patients on day 7 after surgery to evaluate the extent of deep vein thrombosis (DVT)—the primary efficacy outcome of the treatment—in the lower extremities. Preoperative examination for DVTs with US was not performed because the patients had severe pain due to hip fractures. The secondary efficacy outcome was the serum level of D-dimer (Latex Immunoassay; Sysmex, Kobe, Japan) measured on the day of admission, and on days 7 and 14 after HFS.

The primary safety outcome included the incidence of fatal bleeding, bleeding in critical organs (i.e., intracranial bleeding, intraspinal bleeding, or bleeding in any other critical organs), and major bleeding (bleeding requiring

surgical intervention or postoperative loss of hemoglobin >2 g/dl at day 7 or 14 as compared that on day 1). The secondary safety outcome was the incidence of minor bleeding. The volume of fluid drained after HFS was also measured. Minor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding.

Statistical analysis

The Kruskal–Wallis test was used to compare the variables in the groups, and the Mann–Whitney *U* test was used to further compare the variables that showed significant intergroup differences. The Bartlett test was used to examine the uniformity of dispersion of noncategorical variables; analysis of variance (ANOVA) and the Scheffé test were used to compare groups in cases of uniform dispersion, while the Kruskal–Wallis test and the Mann–Whitney *U* test were used to compare groups in cases of nonuniform dispersion. All statistical analyses were performed using the statistical programs Statview (v.5, SAS, Cary, NC, USA) and Statcel2 (OMS, Saitama, Japan). $P < 0.05$ was considered statistically significant.

Results

Baseline data for study subjects

Baseline characteristics did not differ significantly among the groups with regard to age, gender, body mass index (BMI), type of hip fracture (i.e., femoral neck, trochanteric, or subtrochanteric), preoperative duration from injury to surgery, or surgical procedure (Table 2).

Surgical procedures were selected according to the type and instability of the fracture. Hansson pins and femoral head replacement were indicated for femoral neck fractures. Compression hip screws, gamma nails, yen nails, Japanese proximal femoral nail anti-rotations (PFNAs), OM nails, and intramedullary nails were used for trochanteric or subtrochanteric fractures. Drainage tubes for postoperative bleeding were placed at the surgical site in some patients. No significant differences were observed among the groups in terms of intraoperative blood loss or operation time (data not shown).

Effects of FPX and ENO treatment on the incidence of DVT and D-dimer value

The incidence of detected DVT in the FPX group (25.9%) was significantly lower than in the CTRL (65.5%) and ENO (57.1%) groups (Table 3). All of the detected DVTs were asymptomatic in all groups. The incidence of DVT, including the proximal-type DVT (common iliac, femoral, and deep femoral veins) and the distal type (popliteal, calf veins), and the treatment of VTE are shown in Table 3. One case of symptomatic PE—as determined by enhanced computed tomography (CT)—showing decreased saturation of peripheral oxygen (SpO_2) after surgery was seen in the CTRL group. The patient was successfully treated with dose-adjusted unfractionated heparin and vitamin K antagonist.

The levels of D-dimer upon admission showed no significant difference among the groups. However, the values

Table 2 Characteristics of study patients

	CTRL group ($n = 29$)	FPX group ($n = 27$)	ENO group ($n = 28$)
Average age (years)	83.0 ± 7.5	79.7 ± 11.4	82.4 ± 7.4
Men/women	5/24	6/21	6/22
Body mass index (kg/m^2)	20.83 ± 3.76	21.24 ± 4.27	20.68 ± 3.58
Average preop. days	8.7 ± 4.2	8 ± 4.1	9.5 ± 4.1
Creatinine clearance rate (ml/min)	55.2 ± 27.5	61.1 ± 25.4	54.3 ± 18.1
No. of femoral neck fx	7	10	9
No. of trochanteric fx	20	16	17
No. of subtrochanteric fx	2	1	2
Surgical procedures			
Hansson pins	1	1	1
Femoral head replacement	6	9	8
Compression hip screws	2	2	1
Gamma nails	11	11	13
Japanese PFNAs	4	1	1
Yen nails	1	2	2
OM nails	2	0	0
Intramedullary nails	2	1	2

Values are expressed as number of patients or mean ± SD

fx fracture, *PFNA* proximal femoral nail antirotation, *CTRL* control (no intervention), *FPX* fondaparinux, *ENO* enoxaparin

Table 3 Incidence of VTE, treatment, and D-dimer values

Variable	CTRL group ($n = 29$)	FPX group ($n = 27$)	ENO group ($n = 28$)	*P* value CTRL versus FPX	*P* value CTRL versus ENO	*P* value FPX versus ENO
Total DVTs (overlapping)	19 (65.5%)	7 (25.9%)[#,$]	16 (57.1%)	0.003	0.520	0.020
Proximal-type DVTs	4 (13.8%)	1 (3.7%)	2 (7.1%)	0.189	0.418	0.578
Distal-type DVTs	18 (62.1%)	7 (25.9%)[#,$]	15 (53.6%)	0.007	0.519	0.038
Treatments (overlapping)						
Vitamin K antagonist	15	5	10			
LDUH	1	1	0			
Dose-adjusted UH	3	0	1			
IVC filter insertion	1	0	1			
Observation	3	1	4			
Cases with recognized PE	1	0	0			
D-dimer (μg/ml)						
On admission	20.47 ± 15.66	21.73 ± 13.9	18.91 ± 14.97	0.951	0.923	0.783
7 days after HFS	20.48 ± 9.92	11.66 ± 6.13[#]	14.24 ± 8.73[#]	<0.001	0.025	0.529
14 days after HFS	13.61 ± 10.75	7.56 ± 4.99[#]	8.70 ± 5.65	0.014	0.068	0.439

Values are expressed as the number of patients or mean ± SD

VTE venous thromboembolism, *DVT* deep-vein thrombosis, *CTRL* control (no intervention), *FPX* fondaparinux, *ENO* enoxaparin, *LDUH* low-dose unfractionated heparin, *UH* unfractionated heparin, *IVC* inferior vena cava, *HFS* hip fracture surgery

[#] Significantly lower than in the CTRL group

[$] Significantly lower than in the ENO group

of D-dimer in the FPX and ENO groups on day 7 were significantly lower than those in the CTRL group. In addition, FPX even showed significantly lower D-dimer levels on day 14 than in the CTRL group.

Side effects of FPX and ENO treatments

Neither FPX nor ENO gave rise to fatal bleeding causing internal organ failure. However, major bleeding was identified in 2 cases in the FPX group: a small but symptomatic hematoma at the surgical site that required surgical intervention; and a drop in hemoglobin of >2 g/dl that required suspension of FPX administration after 7 days of surgery. In the patient who required surgical intervention, the hematoma was resected under local anesthesia and the wound was re-sutured. Recurrence of hematoma was not observed thereafter, and the wound healed without any trouble. Minor bleeding occurred at the surgical site in 1 patient in the ENO group, which required suspension of ENO administration after 6 days, after which the bleeding stopped within a few days. Postoperative drainage volumes did not differ significantly among the groups, irrespective of the surgical procedure (Table 4).

Discussion

VTE is a common complication after HFS, THA, and TKA [1–7]. Thromboprophylaxis has been recommended to all patients who undergo HFS [1]. FPX is the first synthetic pentasaccharide selective factor Xa inhibitor, and its use was permitted in Japan in April 2007. FPX strongly binds to antithrombin and modifies its conformation, thereby potentiating the natural neutralization of factor Xa by antithrombin. Neutralization of factor Xa interrupts the blood coagulation cascade and inhibits the generation of thrombin [13].

ENO is a type of low-molecular-weight heparin (LMWH) used to prevent VTE; it was approved in France in 1987. LMWHs are fragments of standard heparin produced by either chemical or enzymatic depolymerization and are incapable of binding to thrombin because of their low molecular weights [14]. ENO has been shown to significantly reduce the incidence of DVT after THA [15], and is effective at preventing VTE after HFS [8]. ENO has been approved for use in Japan since 2008. The guidelines of the American College of Chest Physicians (ACCP; 8th edition) recommends the use of FPX and ENO as grade 1A and 1B prophylaxis, respectively, to prevent VTE after HFS [1].

The important studies that compared the efficacies of FPX and ENO include PENTATHLON 2000 [6] and EPHESUS [5], which investigated the efficacy of FPX after THA, and PENTAMAKS [4] and PENTHIFRA [2], which evaluated the efficacies of these agents after TKA and HFS, respectively. Except for PENTATHLON 2000, all of the studies reported that the incidences of VTE after treatment with FPX were significantly lower than those after

Table 4 Drainage volume and side effects

Variable	CTRL group ($n = 29$)	FPX group ($n = 27$)	ENO group ($n = 28$)	*P* value CTRL versus FPX	*P* value CTRL versus ENO	*P* value FPX versus ENO
Drainage volume (ml)						
Postop. 1 day to tube removal	71.4 ± 63.0	83.8 ± 90.8	74.9 ± 76.9	0.932	0.994	0.963
Total volume	248.8 ± 173.7	250.1 ± 214.6	242.5 ± 183.9	0.999	0.996	0.993
Osteosynthesis	132.8 ± 67.1	192.6 ± 209.9	206.3 ± 178.3	0.758	0.672	0.984
Femoral head replacement	403.5 ± 147.8	368.3 ± 241.7	283.1 ± 193.4	0.948	0.562	0.698
Side effects (no. of cases)						
Fatal bleeding	0	0	0			
Major bleeding	0	2	0			
Minor bleeding	0	0	1			
Total	0	2	1			

Values are expressed as number of patients or mean ± SD

CTRL control (no intervention), *FPX* fondaparinux, *ENO* enoxaparin

treatment with ENO [6]. In 2 prospective nonrandomized studies in Japan, Fuji and Fujita [7, 8] reported the incidences of VTE to be 21.6 and 14.0% in patients who received FPX or ENO after HFS. However, to the best of our knowledge, this is the first prospective study to directly compare the efficacies of FPX and ENO after HFS in a Japanese population.

We found that the incidence of VTE in the FPX group (25.9%) was similar to that reported by previous studies [7], while the incidence of VTE in the ENO group was higher than that in previous studies [2, 8]. These discrepancies can be attributed to differences in patient backgrounds, differences in the evaluation method used for VTEs [venography (VG) was used in previous studies] [7, 8], and the use of low doses of ENO in Japan as compared to Western countries [16, 17]. Additionally, 7 patients (25%) in this study received only 2000 IU of ENO according to their Ccr values.

Several imaging procedures to detect DVTs have been reported [18–21]. The procedure adopted in this study afforded higher sensitivity (89%) and specificity (97%) in detecting VTE [20] and eliminated the need for a radiocontrast agent, thereby eliminating the possibility of adverse effects [19]. Alternatively, enhanced CT can identify thrombi easily throughout the deep venous system from the inferior vena cava to calf veins [18]. However, enhanced CT may have a limitation in the detection of distal-type DVTs [9]. Thus, we performed enhanced CT only in cases of suspected symptomatic PE or in patients showing high preoperative D-dimer values. In this study, 34 patients exceeded the preoperative cut-off value of D-dimer, which was set at 20 μg/ml. This cut-off value was determined according to the previously published study [9]. Among these patients, preoperative DVT was found in only one case (2.9%) with enhanced CT, and this case was excluded from the study, as we mentioned in the section on exclusion criteria. VG is believed to be the most reliable method of detecting DVTs. However, the procedure is invasive and may not be practical for common clinical use [9]. In addition, since the lower limb venous system shows many variations [22], and excellent anatomical knowledge is required for accurate evaluation with VG, we did not use VG.

The plasma concentration of D-dimer indicates the presence of fibrin dissolution products (FDP), thereby selectively indicating the dissolution of fibrin. Perrier et al. [23] stated that a normal D-dimer concentration could rule out VTE. D-dimer can thus be a potent indicator for the absence or presence of VTE [10, 11]. In our previous study, D-dimer values in FPX-treated patients were significantly lower than those in the untreated HFS patients [9]. However, no study has evaluated the efficacies of FPX and ENO on the basis of D-dimer levels. The present study demonstrated that both FPX and ENO resulted in significantly lower D-dimer values as compared to controls.

The overall incidence rate of side effects after FPX treatment in Japan is reported to be 1.13%, with serious side effects occurring in 0.27% (i.e., bleeding from intestinal organs, 11 cases; bleeding from surgical sites, 33 cases). In addition, 2 fatal cases have been reported: 1 with bleeding from the colon and another with cerebellum hemorrhage. The reported overall side effect incidence after ENO treatment is 1.08% in Japan, with serious side effects occurring in 0.26% (i.e., thrombocytopenia, 3 cases; bleeding from the surgical site, 1 case). However, no fatal cases have been reported. These data were obtained from an aftermarket investigation performed by the suppliers (FPX; GlaxoSmithKline, Tokyo, Japan, and ENO; Sanofi-Aventis, Tokyo, Japan): the side effects were reported voluntarily by doctors, and the estimated numbers of

administrated patients were 23,000 in FPX (19,000 in 2.5 mg and 4000 in 1.5 mg, respectively) and 3900 in ENO. Our results showed 1 case of minor bleeding in the ENO group and 2 cases of major bleeding in the FPX group. These data indicate that FPX has a higher rate of serious side effects than ENO. We previously reported that the incidence of side effects under FPX treatment without evaluating Ccr was 10.5% [9], which was higher than other reports [2, 3, 7]. In the present study, to reduce side effects, we determined the administration doses based on the values of Ccr, age, and body weight. However, two patents (7.4%) in the FPX group showed major bleeding. To minimize side effects, the Ccr, age, and body weight thresholds for administration doses should be re-evaluated and determined in future studies.

Fuji et al. [24] reported the efficacy of ENO after THA and TKA with three dosage regimen studies, and concluded that the twice daily administration of 20 mg of ENO (equivalent to 2000 IU of ENO) is effective at preventing VTE in Japanese patients. In the present study, no significant difference was observed in the incidence of VTE in patients administered 4000 IU of ENO (66.7%) versus 2000 IU (42.9%) in patients with a Ccr of 30–50 ml/min. Thus, a lower dose may be sufficient for preventing VTE, and it would be cost effective. Further research to determine the appropriate doses of ENO for patients (especially those with Ccr 30–50 ml/min) is also required.

The limitations of this study should be noted. In the present study, screening for preoperative DVT was performed with the D-dimer values at baseline (>20 μg/ml) [9], followed by enhanced CT for suspected patients. However, the actual incidence of DVT at baseline might not be determined according to our study protocol. Because the D-dimer value is known to be higher at the time of injury [21], it is difficult to establish the preoperative cut-off D-dimer value for patients with hip fractures. Although preoperative imaging diagnoses for all patients may help to determine the actual incidence of DVT at baseline, evaluating the DVT (especially distal type) with US is a very difficult task in patients with hip fractures because of the pain under examination and the patient's positioning. Enhanced CT also exhibits limitations in detecting distal-type DVTs [9]. However, unless the actual incidence of DVT is observed at baseline, the incidence rates after treatment are not fully comparable. In this regard, combining preoperative screening with enhanced CT or US and routine postoperative examinations with US may be better option for analyzing the actual incidence of VTE in future studies.

In summary, this prospective study compared the incidence of VTE and side effects of FPX or ENO administration after HFS in a Japanese population. FPX was superior to ENO in suppressing VTE after HFS. However, FPX treatment resulted in a higher incidence of side effects, including major bleeding.

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References

1. Geerts WH, Bergquist D, Pineo GF, Heit JA, Samama CF, Lassen MR, Colwell CW. Prevention of venous thromboembolism. American College of Chest Physicians evidence-based clinical guidelines (8th edition). Chest. 2008;133:381S–453S.
2. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298–304.
3. Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery. A multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2003;163:1337–42.
4. Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305–10.
5. Lassen MR, Bauer KA, Eriksson BI, Turpie AGG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet. 2002;359:1715–20.
6. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet. 2002;359:1721–6.
7. Fuji T, Fujita S. Efficacy and safety of fondaparinux sodium for the prevention of venous thromboembolism after hip-fracture surgery. Kossetsu (Fracture). 2008;30:206–9 (in Japanese).
8. Fuji T, Fujita S. Efficacy and safety of enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. Hip Joint. 2008;34:679–82 (in Japanese).
9. Sasaki S, Miyakoshi N, Matsuura H, Saitoh H, Kudoh D, Shimada Y. Prospective randomized controlled trial on the effect of fondaparinux sodium for the prevention of venous thromboembolism after hip fracture surgery. J Orthop Sci. 2009;14:491–6.
10. Bongard O, Wicky J, Peter R, Simonovska S, Vogel JJ, Moerloose P, Bounameaux H. D-dimer plasma measurement in patients undergoing major hip surgery: use in the prediction and diagnosis of postoperative proximal vein thrombosis. Thromb Res. 1994;74:487–93.
11. Peetz D, Hafner G, Hansen M, Mayer A, Rippin G, Rommens PM, Prellwitz W. Dose-adjusted thrombosis prophylaxis in trauma surgery according to levels of D-dimer. Thromb Res. 2000;98:473–83.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
13. Turpie AGG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med. 2001;344:619–25.

14. Hirsh J, Levine MN. Low molecular weight heparin. Blood. 1992;79:1–17.
15. Turpie AGG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, Andrew M, Hull RD, Gent M. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med. 1986;315:925–9.
16. Barsotti J, Gruel Y, Rosset P, Favard L, Dabo B, Andreu J, Delahousse B, Leroy J. Comparative double-blind study of two dosage regimens of low-molecular weight heparin in elderly patients with a fracture of the neck of the femur. J Orthop Trauma. 1990;4:371–5.
17. Thaler HW, Roller RE, Greiner N, Sim E, Korninger C. Thromboprophylaxis with 60 mg enoxaparin is safe in hip trauma surgery. J Trauma. 2001;51:518–21.
18. Kim T, Murakami T, Hori M, Kumano S, Sakon M, Nakamura H. Efficacy of multi-slice helical CT venography for the diagnosis of deep vein thrombosis: comparison with venous sonography. Radiat Med. 2004;22:77–81.
19. Lensing AWA, Prandoni P, Büller HR, Casara D, Cogo A, Cate JWT. Lower extremity venography with iohexol: results and complications. Radiology. 1990;177:503–5.
20. Pedersen OM, Aslaksen A, Vik-Mo H, Bassoe AM. Compression ultrasonography in hospitalized patients with suspected deep venous thrombosis. Arch Intern Med. 1991;151:2217–20.
21. Shiota N, Satoh T, Matsuo M, Kajiya M, Sakata K, Inoue H. A study of postoperative deep-vein thrombosis in proximal femoral fracture. Rinsho Seikeigeka (Clin Orthop Surg). 2003;38:593–9 (in Japanese).
22. Quinlan DJ, Alikhan RA, Gishen P, Sidhu PS. Variations in lower limb venous anatomy: implications for US diagnosis of deep vein thrombosis. Radiology. 2003;228:443–8.
23. Perrier A, Desmarais S, Miron MJ, Moerloose P, Lepage R, Slosman D, Didier D, Unger PF, Patenaude JV, Bounameaux H. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet. 1999;353:190–5.
24. Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. J Orthop Sci. 2008;13:442–51.