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Research article

Incidences of deep vein thrombosis and major bleeding under the administration of fondaparinux for thromboprophylaxis after periacetabular osteotomy: a retrospective observational study

Kensuke Fukushima[1*], Hiroki Saito[1], Tomohisa Koyama[1], Yoshihisa Ohashi[1], Katsufumi Uchiyama[2], Naonobu Takahira[3] and Masashi Takaso[1]

[1]Department of Orthopaedic Surgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara 252-0374, Japan, [2]Department of Patient Safety and Healthcare Administration, Kitasato University School of Medicine, 1-15-1 Kitasato, Sagamihara 252-0374, Japan and [3]Department of Rehabilitation, Kitasato University School of Allied Health Sciences, 1-15-1 Kitasato, Minami-ku, Sagamihara 252-0329, Japan

*Correspondence to: K. Fukushima. E-mail: kenfu@r4.dion.ne.jp

ABSTRACT

Periacetabular osteotomy (PAO) is an effective joint-preserving procedure for patients with developmental dysplasia of the hip. Although deep vein thrombosis (DVT) is considered a serious complication of orthopaedic surgery, there is no consensus regarding a thromboprophylaxis strategy after PAO. We have routinely administered fondaparinux for DVT prophylaxis in adult patients undergoing PAO. The aim of this study was to investigate the incidences of DVT and major bleeding under the administration of fondaparinux for thromboprophylaxis after PAO. A total of 95 patients (100 hips) who underwent PAO with post-operative administration of fondaparinux for thromboprophylaxis were retrospectively enrolled. The incidences of DVT on ultrasound, major bleeding, and administration cessation were evaluated. Asymptomatic DVT occurred in one patient, major bleeding occurred in 14 hips and the administration of fondaparinux was stopped in 17 hips. Given the observed incidence of major bleeding, safer DVT prophylaxis modalities should be considered during PAO.

INTRODUCTION

Developmental dysplasia of the hip (DDH) is characterized by a shallow, obliquely oriented acetabulum. Anterior and/or lateral undercoverage in DDH results in significantly elevated contact pressures, reduced contact area and joint instability; this remains one of the more frequent causes of secondary osteoarthritis of the hip. As such, various acetabular reorientation operations have been indicated for patients with DDH. Particularly, periacetabular osteotomy (PAO) provides excellent radiographic and clinical results and is the most widely used surgical procedure for patients with DDH [1, 2].

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are considered to be serious complications of orthopaedic surgery, especially in the lower extremities, potentially resulting in significant morbidity and mortality [3]. Several guidelines aimed at preventing DVT and PE have recommended the administration of anticoagulant drugs, based on imaging studies that show their efficacy for reducing the incidence of DVT, including asymptomatic DVT [4, 5]. Based on a recent review, the incidence of DVT after PAO ranges from 0 to 2.1% [6]. However, relatively few reports have assessed DVT related to hip preservation surgery, compared to that for total hip arthroplasty (THA). Since the majority of patients who undergo hip preservation surgery are young and healthy and may not be considered at high risk for DVT, there is no consensus regarding the most effective and safe method for DVT prophylaxis in PAO.

Under the current insurance policies in Japan, only fondaparinux can be administered as an anticoagulant drug during PAO. We have routinely administered fondaparinux for DVT prophylaxis in adult patients undergoing PAO. Although the administration of fondaparinux for DVT prophylaxis is useful, bleeding complications have been described [7]. In the present study, therefore, we aimed to investigate the incidences of DVT and major bleeding under the administration of fondaparinux for thromboprophylaxis after PAO.

PATIENTS AND METHODS

Patients

We obtained approval from our institutional review board for this study, and it was performed in accordance with the ethical

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Table I. Demographics of the patient population

Age (years)	40.6 ± 8.4
Sex	Male: 2 hips (2%)
	Female: 98 hips (98%)
BMI (kg/m^2)	23.1 ± 3.8
Administration of anticoagulants	(+): 0 hips
	(−): 100 hips
DVT risk factors	(+): 8 hips
	(−): 92 hips

BMI, body mass index; DVT, deep vein thrombosis.

standards laid down in the 1964 Declaration of Helsinki and its later amendments.

We have routinely administrated fondaparinux as the first choice for DVT prophylaxis in adult patients undergoing PAO since 2010. At the same time, we began screening for DVT with ultrasound and measuring D-dimer levels. We retrospectively enrolled 131 consecutive patients (140 hips) who underwent PAO between January 2010 and June 2020. All patients were Asian. Patients who were not able to undergo ultrasound pre-operatively and post-operatively (18 hips), those aged 20 years or younger (11 hips) and those who post-operatively received anticoagulant therapy other than the administration of fondaparinux (11 hips) were excluded. Accordingly, 95 patients (100 hips) were finally included in this study.

For all included patients, data regarding age, sex, body mass index (BMI) and the pre-operative administration of anticoagulants, as well as pre-operative comorbidities and the medical history on known risk factors of DVT (e.g. cardiovascular disease, diabetes mellitus, cancer, and a history of DVT and PE) [8], were retrospectively collected from the clinical records. Recorded demographic data of the patients are displayed in Table I.

We performed curved periacetabular osteotomy (CPO), developed by Naito and colleagues [9, 10], in all cases. Epidural anaesthesia with or without general anaesthesia was used. CPO is based on a modification of the Bernese PAO and involves minimally invasive exposure and a spherical osteotomy to easily move the osteotomized fragment. Consequently, CPO can be utilized to achieve earlier rehabilitation and fewer complications compared to those with Bernese PAO [9]. We performed autologous blood transfusion in all cases. All patients were permitted to move to a wheelchair on the day after surgery. One-third partial weight-bearing was permitted at 3 weeks post-operatively, and full weight-bearing was permitted after the confirmation of bone union (∼10 weeks post-operatively).

For thromboprophylaxis, a once-daily subcutaneous dose of 2.5 mg of fondaparinux was administered from post-operative day 1 to post-operative day 14. The course was underlying a package insert. The haemoglobin (Hb) level was investigated on post-operative days 1, 3, 7 and 14. Physicians could stop the administration of fondaparinux by their own decision at any time. All patients were used bilateral anti-embolism compression stockings during hospitalization as mechanical prophylaxis.

Diagnosis of DVT

Duplex ultrasonography of the bilateral common femoral, superficial, popliteal and calf veins was performed pre-operatively and on post-operative day 7 to confirm a clinical diagnosis of DVT. The criteria for the diagnosis of DVT were as follows: a loss of compressibility of the vein, presence of intraluminal echogenicity and absence of venous flow. DVT was classified as proximal or distal. All patients with a diagnosis of DVT underwent a PE survey using helical computer tomography (CT). Additionally, D-dimer levels were measured pre-operatively and on post-operative days 1, 3, 7 and 14.

Diagnosis of major bleeding

From clinical records, the incidences of major bleeding and fondaparinux administration cessation were reviewed. Additionally, the reasons for the cessation of administration were investigated. Major bleeding was diagnosed on the basis of the following criteria, as in previous publications: fatal bleeding; bleeding that was retroperitoneal, intracranial, intraspinal, or involving any other critical organ; bleeding leading to reoperation; and a reduction in the Hb level >2 g/dL on post-operative days 3, 7 or 14, compared to that on post-operative day 1 [11].

Statistical analyses

Statistical analyses were performed using JMP version 11.0 software (SAS Institute, Cary, NC). Results are expressed as the mean and standard deviation of the mean, unless otherwise indicated. Hb and D-dimer levels were compared between post-operative days 1, 3, 7 and 14 using the non-parametric Mann–Whitney *U* test. Additionally, the demographic data, Hb and D-dimer levels were statistically compared between the patients with major bleeding and without major bleeding. *P*-values <0.05 were considered statistically significant.

RESULTS

Among the 100 hips enrolled in this study, one hip (1%) was clinically diagnosed with DVT. The patient was a 55-year-old woman without any risk factors related to DVT. The patient was asymptomatic, and the DVT was classified as distal. In addition, the patient clinically diagnosed with DVT did not have PE, as confirmed by a CT survey.

With the exception of a slight decrease at 3 days post-operatively, the mean D-dimer level gradually increased, reaching a maximum of 7.9 ± 3.5 at 14 days post-operatively (Fig. 1). The mean Hb level decreased gradually until 7 days post-operatively, with a noted recovery at 14 days post-operatively (Fig. 2).

Major bleeding occurred in 14 hips (14%). There were no cases of fatal bleeding or bleeding that was retroperitoneal, intracranial, intraspinal or involving any other critical organ. Furthermore, no cases required reoperation. Details of the patients with major bleeding and without bleeding are shown in Table II. The mean age and BMI were not statistically significant between two groups. Although the mean level of Hb at pre-operative and 1 day post-operatively were not statistically significant between two groups, significant decrease was identified at 3 days post-operatively. The administration of fondaparinux was stopped in 17 cases (17%); the reasons for which are shown in Table III. In 12 cases (70.6%), the administration of fondaparinux was stopped due to concerns regarding anaemia. All patients showed

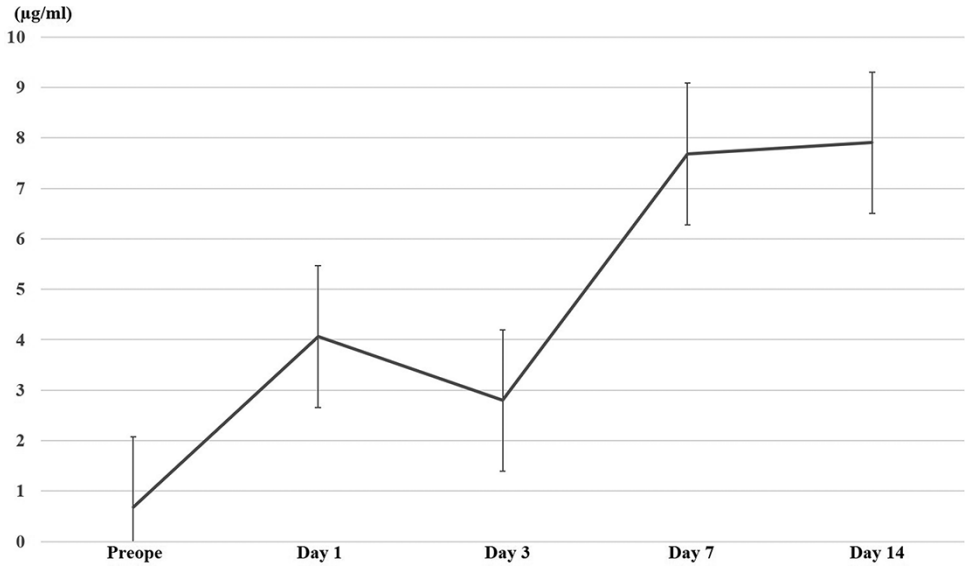

Fig. 1. Time course of the mean D-dimer level. Pre-ope: pre-operative.

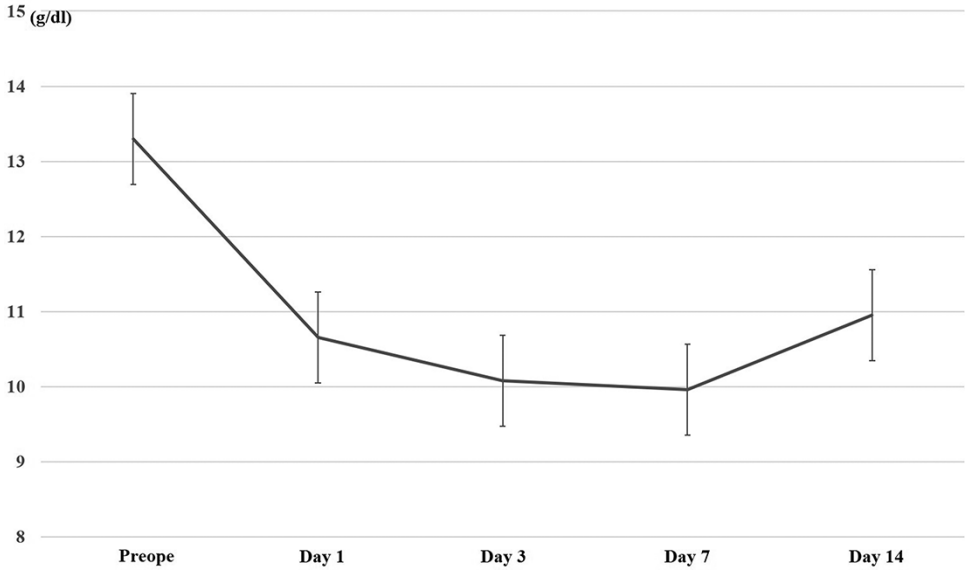

Fig. 2. Time course of the mean Hb level. Pre-ope: pre-operative.

increasing Hb levels after stopping the administration of fondaparinux. In two cases (11.8%), we identified hematoma and discharge at the surgical site. However, the sites were not infectious. The hematoma was not increased, and the discharge was stopped almost 1 week after stopping the administration. We did not need the additional treatment for the surgical site.

DISCUSSION

In this study, we found that the administration of fondaparinux for thromboprophylaxis after PAO may have more risks than benefits. PAO is one of the preferred surgical procedures that can realize biomechanical and anatomical reconstruction in patients with DDH. Although some complications related to PAO have been reported [1, 12], few reports have focused on DVT during PAO. In a study by Zaltz *et al.*, the incidence of DVT among 1067 PAOs with various DVT prophylaxis protocols, such as mechanical only, chemical only, or the combination of mechanical and chemical strategies, was 0.66% (7/1067 procedures) [13]. Polkowski *et al.* evaluated the incidence of DVT in 149 hips treated by PAO with aspirin administration and mechanical compression for prophylaxis, using the same assessment as that in the present study (ultrasound screening at 1-week post-operatively) [14]. In their results, two hips (1.3%) that were negative on post-operative screening by ultrasound had identifiable DVT, with clinical symptoms on post-operative days 14 and 34, respectively. Consequently, the authors concluded that routine post-operative screening after PAO should not be recommended because of the low frequency of DVT occurrence after PAO. The incidence of DVT after PAO in the current study was comparable to that in previous studies, with only one case (1%) of asymptomatic DVT. Furthermore, the incidence of DVT after

Table II. Details of the patients with major bleeding and without major bleeding

	With major bleeding (n = 14)	*Without major bleeding (n = 86)*	*P-value*
Age (years)	41.0 ± 11	40.5 ± 8.0	0.51
BMI (kg/m^2)	21.7 ± 2.0	23.3 ± 4.0	0.37
Pre-operative Hb (g/dl)	13.4 ± 0.96	13.3 ± 0.97	0.54
P.O. day 1 Hb (g/dl)	11.2 ± 1.4	10.6 ± 1.4	0.32
P.O. day 3 Hb (g/dl)	8.98 ± 1.5	10.3 ± 1.6	0.0071*
P.O. day 7 Hb (g/dl)	8.4 ± 1.4	10.2 ± 1.5	0.0002*
P.O. day 14 Hb (g/dl)	9.5 ± 1.3	11.2 ± 1.2	<0.0001*
Pre-operative D-dimer (μg/ml)	0.69 ± 0.4	0.68 ± 0.28	0.54
P.O. day 1 D-dimer (μg/ml)	6.40 ± 7.8	3.71 ± 2.7	0.19
P.O. day 3 D-dimer (μg/ml)	3.52 ± 1.4	2.68 ± 0.79	0.049*
P.O. day 7 D-dimer (μg/ml)	8.65 ± 2.2	7.54 ± 2.9	0.11
P.O. day 14 D-dimer (μg/ml)	11.5 ± 2.6	7.33 ± 0.28	<0.0001*

*P<0.05.
BMI, body mass index; Hb, haemoglobin; P.O., postoperative.

Table III. The reasons for the cessation of fondaparinux administration

Anaemia	12 hips (70.6%)
Increase in serum aminotransferase level without symptoms	3 hips (17.6%)
Hematoma and discharge at the surgical site	2 hips (11.8%)

THA with the administration of fondaparinux for prophylaxis has been evaluated in several studies. In the study by Yokote *et al.*, 6 of 84 Asian patients (7.1%) who underwent THA with the administration of fondaparinux for prophylaxis were diagnosed with asymptomatic DVT [15]. In addition, Fukushima *et al.* reported that the incidence of DVT (assessed by a screening ultrasound) related to hip arthroscopic surgery without prophylaxis was 6.94% [16]. Thus, the incidence of DVT after PAO was lower in the present study than not only the incidence of DVT related to THA, but also the incidence of DVT related to hip arthroscopy. As DVT and PE can be serious life-threatening complications, we consider it important to investigate asymptomatic DVT because it is difficult to diagnose and can potentially develop into symptomatic DVT and PE. However, we might have to agree with the opinion expressed in Polkowski *et al.* [14].

Fondaparinux, a selective inhibitor of factor Xa, is indicated for the prophylaxis of DVT after total joint arthroplasty of the lower extremities [4]. Studies comparing fondaparinux to low-molecular-weight heparin have shown its usefulness for thromboprophylaxis [17, 18]. Nagase *et al.* reported that the prevalence of PE after total knee arthroplasty and THA was significantly reduced when fondaparinux was used in combination with mechanical prophylaxis, compared to that with the use of mechanical prophylaxis alone [19]. In Japan, since 2010, the use of fondaparinux is covered by insurance when administered for thromboprophylaxis after total joint arthroplasty of the lower extremities, hip fracture surgery and osteotomy around the hip joint. Therefore, we have routinely administered fondaparinux for DVT prophylaxis in adult patients undergoing PAO. To our best knowledge, the current study is the first to assess the incidence of DVT under the administration of fondaparinux for thromboprophylaxis after PAO. As described before, the incidence of DVT in the current study was lower than the incidences of DVT after THA and hip arthroscopic surgery. However, the incidence of DVT was comparable to that in studies indicating the effectiveness of other thromboprophylaxis protocols [6, 13, 14, 20].

Bleeding complications associated with the use of fondaparinux have been described [7, 11]. According to an aftermarket investigation of fondaparinux in Japan, the overall incidence of side effects following fondaparinux treatment was 1.13%, with serious side effects occurring in 0.27% of cases (bleeding from intestinal organs, 11 cases; bleeding from surgical sites, 33 cases) [21]. Thus, several studies have cautioned against the use of fondaparinux because of the possibility of bleeding complications [22–24]. In the present study, major bleeding occurred in 14% of patients. Compared between the patients with major bleeding and without major bleeding, a significant decrease of Hb level was identified at 3 days post-operatively. Since we administrated fondaparinux from post-operative day 1, we thought that the administration of fondaparinux directly affected the major bleeding. Furthermore, we could not clarify the patients' characteristics who occur major bleeding in this study. In a review by Aali Rezaie *et al.*, there were no reports of major bleeding as a complication for any type of prophylaxis after PAO [6]. Recently, Azvoy *et al.* reported that the administration of aspirin to patients undergoing PAO was safe and effective in minimising the risk of DVT [25]. In addition, Kraeutler *et al.* reported that the use of a portable, mechanical compression device and low-dose aspirin effectively lessens the risk of DVT, without increasing the risk of bleeding complications [26].

The current study has several limitations to acknowledge. First, as a major limitation, we did not perform any comparisons to patients who did not receive thromboprophylaxis treatment or received a different thromboprophylaxis treatment. Therefore, the incidences of DVT and major bleeding in the current study cannot be unequivocally attributed only to the administration of fondaparinux. Since we started the administration of fondaparinux and screening for DVT with ultrasound at the same time, we could not set an appropriate control group. Therefore, further studies are needed. Second, the current study was performed retrospectively; therefore, the decision-making criteria for the cessation of fondaparinux administration differed by a physician. The course and characteristics of patients who stopped the administration were not standardized. Third, we performed post-operative clinical diagnosis of DVT only with ultrasound on post-operative day 7. We might underestimate the incidence of DVT.

In conclusion, given the incidence rate of major bleeding observed in the current study, we should consider safer DVT prophylaxis modalities than the administration of fondaparinux during PAO.

DATA AVAILABILITY

The data underlying this article cannot be shared publicly due to privacy concerns.

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CONFLICT OF INTEREST STATEMENT

All authors declare that no benefits in any form that are related directly or indirectly to the subject of this manuscript have been or will be received from a commercial party.

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