Incidence 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
Table I. Demographics of the patient population

| Age (years) | 40.6 ± 8.4 |
|---|---|
| Sex | Male: 2 hips (2%) Female: 98 hips (98%) |
| BMI (kg/m²) | 23.1 ± 3.8 |
| Administration of anticoagulants | (+): 0 hips (-): 100 hips (+): 8 hips (-): 92 hips |
| DVT risk factors | 8 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 fon-
daparinux 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...
Incidence of DVT and major bleeding with fondaparinux after PAO

• 295

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
The reasons for the cessation of fondaparinux administration

| Reason                                      | With major bleeding (n=14) | Without major bleeding (n=86) | P-value |
|---------------------------------------------|-----------------------------|-------------------------------|---------|
| Anaemia                                     | 12 hips (70.6%)             |                               |         |
| Increase in serum aminotransferase level     | 3 hips (17.6%)              |                               |         |
| Hematoma and discharge at the surgical site | 2 hips (11.8%)              |                               |         |

*P<0.05.

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

| Parameter                              | 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/m²)                            | 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.

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 after-market 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.

ACKNOWLEDGEMENTS
We would like to thank Editage (www.editage.com) for English language editing.

FUNDING
None declared.

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.

REFERENCES
1. Clohisy JC, Schutz AL, St John L et al. Periacetabular osteotomy: a systematic literature review. Clin Orthop Relat Res 2009; 467: 2041–52.
2. Tibor LM, Sink EL. Periacetabular osteotomy for hip preservation. Orthop Clin North Am 2012; 43: 343–57.
3. Kanchanabat B, Stepotavrat W, Meknavin S et al. Systematic review and meta-analysis on the rate of postoperative venous thromboembolism in orthopaedic surgery in Asian patients without thromboprophylaxis. Br J Surg 2011; 98: 1356–64.
4. Falck-Ytter Y, Francis CW, Johanson NA et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis: 9th ed: American College of Chest Physicians Evidenced-Based Clinical Practice Guidelines. Chest 2012; 141: e2785–325.
5. Struijk-Mulder MC, Ettema HB, Verheyen CC et al. Comparing consensus guidelines on thromboprophylaxis in orthopedic surgery. J Thromb Haemost 2010; 8: 678–83.
6. Aali Razia A, Azboy I, Parvizi J. Venous thromboembolism prophylaxis after hip preservation surgery: a review and presentation of institutional experience. J Hip Preserv Surg 2018; 5: 181–9.
7. Tsuda K, Nishii T, Sakai T et al. Thromboprophylaxis with low-dose, short-term fondaparinux after elective hip surgery. J Thromb Haemost 2016; 41: 413–21.
8. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Haemost 2016; 41: 3–14.
9. Naito M, Shiramizu K, Akiyoshi Y et al. Curved periacetabular osteotomy for treatment of dysplastic hip. Clin Orthop Relat Res 2005; 433: 129–35.
10. Naito M, Nakamura Y. Curved periacetabular osteotomy for the treatment of dysplastic hips. Clin Orthop Surg 2014; 6: 127–37.
11. Yukizawa Y, Inaba Y, Watanabe S et al. Plasma accumulation of fondaparinux 2.5 mg in patients after total hip arthroplasty. J Thromb Thrombolysis 2012; 34: 526–32.
12. Hawrani D, Sucato DJ, Podeszwa DA et al. Complications associated with the Bernese periacetabular osteotomy for hip dysplasia in adolescents. J Bone Joint Surg Am 2010; 92: 1707–14.
13. Zaltz I, Beaule P, Clohisy J et al. Incidence of deep vein thrombosis and pulmonary embolus following periacetabular osteotomy. J Bone Joint Surg Am 2011; 93: 62–5.
14. Polkowski GG, Duncan ST, Bloemke AD et al. Screening for deep vein thrombosis after periacetabular osteotomy in adult patients: is it necessary? Clin Orthop Relat Res 2014; 472: 2500–5.
15. Yokote R, Matsubara M, Hirasawa N et al. Is routine chemical thromboprophylaxis after total hip replacement really necessary in a Japanese population? J Bone Joint Surg Br 2011; 93: 251–6.
16. Fukushima K, Takahira N, Uchiyama K et al. The incidence of deep vein thrombosis (DVT) during hip arthroscopic surgery. Arch Orthop Trauma Surg 2016; 136: 1431–5.
17. Turpie AG, Gallus AS, Hoek JA. Pentasaccharide investigators. A synthetic pentasaccharide for prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 2001; 344: 619–25.
18. Turpie AG, Bauer KA, Eriksson BI et al. 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.
19. Nagase Y, Yasunaga H, Horiguchi H et al. Risk factors for pulmonary embolism and the effects of fondaparinux after total hip and knee arthroplasty: a retrospective observational study with use of a national database in Japan. J Bone Joint Surg Am 2011; 93: e146.
20. Sugano N, Miki H, Nakamura N et al. Clinical efficacy of mechanical thromboprophylaxis without anticoagulant drugs for elective hip surgery in a national population. J Arthroplasty 2009; 24: 1254–7.
21. Sasaki S, Miyakoshi N, Matsuura H et al. Prospective randomized controlled trial on the effect of fondaparinux sodium for prevention of venous thromboembolism after hip fracture surgery. J Orthop Sci 2009; 14: 491–6.
22. Hannon MG, Lamont JG. Compartment syndrome due to massive leg hematoma after primary total hip arthroplasty: a previously unreported complication of fondaparinux. J Arthroplasty 2012; 27: 1414.e9–11.
23. Hur M, Park SK, Koo CH et al. Comparative efficacy and safety of antiocoagulants for prevention of venous thromboembolism after hip and knee arthroplasty. Acta Orthop 2017; 88: 634–41.
24. Fuji T, Fujita S, Ochi T. Fondaparinux prevents venous thromboembolism after replacement surgery in Japanese patients. Int Orthop 2008; 32: 443–51.
25. Azboy I, M Kheir M, Huang R et al. Aspirin provides adequate VTE prophylaxis for patients undergoing hip preservation surgery, including periacetabular osteotomy. J Hip Preserv Surg 2018; 5: 125–30.
26. Kraeutler MJ, Raju S, Garabekyan T et al. Incidence of deep venous thrombosis following periacetabular and derotational osteotomy: a case for mechanical prophylaxis. J Hip Preserv Surg 2018; 5: 119–24.