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Original Article

A comparison of indobufen and low-molecular-weight heparin in the prevention of deep vein thrombosis in patients after total hip arthroplasty: a prospective randomized controlled study

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Abstract: Objective: This was a prospective, randomized, controlled study to explore the anti-coagulation effectiveness and drug safety of indobufen in patients with total hip arthroplasty. Methods: Patients with avascular necrosis of the femoral head (AVN), hip traumatic arthritis (OA), and developmental dysplasia of the hip (DDH) who had an indication for total hip arthroplasty (THA) and who were admitted to our hospital from January to December 2017 were analyzed in this study. This study was a prospective, single-center, randomized controlled study. Eligible patients were randomized and divided into two groups: the LMWH group and the INDO group. For the LMWH group, low-molecular-weight heparin calcium was given by subcutaneous navel injection at a dose of 4100u per day. For the INDO group, indobufen was administered orally at a dose of 200 mg bid. All the anticoagulants were continuously used no fewer than 35 days postoperatively. The primary outcomes were morbidity and the severity of deep vein thrombosis (DVT). Results: A total of 216 patients were available. 50 (23.15%) patients developed DVTs. In the LWMH group, 28 patients had DVTs, including 21 patients with DVTs in their intermuscular veins, 5 patients with DVTs in their peroneal and posterior tibial veins, 1 patient with DVTs in his or her popliteal veins, and 1 patient with DVTs in his or her femoral veins. In the INDO group, 22 patients had DVTs, including 19 patients with DVTs in their intermuscular veins, 3 patients with DVTs in their peroneal and posterior tibial veins, but no patient had DVTs in their popliteal or femoral veins. The morbidity and severity showed no statistical differences between the two groups. The volume of drainage was 671.62 ± 273.23 ml in the first two days postoperatively in the LWMH group, and 818.82 ± 346.22 ml in the INDO group. The volume of drainage in the INDO group was significantly higher than in the LWMH group ($P = 0.001$). The fall in blood hemoglobin within the first 10 days postoperatively was 8.25 ± 5.35 g/L in the LWMH group and 9.63 ± 6.23 g/L in the INDO group respectively, with no statistical difference ($P = 0.136$). In this study, no major bleeding event occurred in either group. In the LMWH group, there was 1 patient with coagulation system complications (ecchymosis), 1 patient with other complications (erythra). In the INDO group, there were 3 patients with digestive complications (nausea, vomiting, abdominal pain, and distention), but no other complication was found. The morbidity and classification showed no statistical differences between the two groups ($\chi^2 = 4.970$, $P = 0.174$). Conclusions: Compared with LMWH, indobufen had a similar effect on the prevention of DVTs in patients with primary THA. The morbidity and severity showed no significant differences between the two groups. In addition, no major bleeding events occurred in this study.

Keywords: Indobufen, deep vein thrombosis, total hip arthroplasty, anticoagulants

Introduction

Deep vein thrombosis (DVT) is a major medical problem characterized by thrombi formation in the deep venous system that can result in a fatal pulmonary embolism (PE). In the United States, DVT and PE result in up to 600,000 hospitalizations a year, and nearly 50,000 individuals die annually as a result of PE [1]. Complications of DVT may affect large numbers of patients, especially orthopedic patients, as the incidence of hospital-acquired DVT after major orthopedic surgery is 40% to 60% [2, 3]. Once the patient develops DVT, there is a large

economic burden with a health care cost up to $33,200 per patient [4, 5]. Thus, prevention is essential when treating patients with high risk of DVT, and it may lead to a substantial reduction in overall perioperative morbidity, mortality, and the health care cost burden.

Common drugs for DVT prevention include low molecular weight heparin (LMWH), new oral anticoagulants (NOACs), Warfarin and unfractionated heparin (UFH) [2, 6]. For the consideration of convenience [3, 7] and safety [8], the former two were commonly used in daily clinical practices. LMWH decreases the risk of DVT by 50% to 60% and the risk of PE by approximately two-thirds [8, 9]. NOACs, including apixaban, dabigatran, edoxaban and rivaroxaban, have a similar or better clinical effect on the treatment and prevention of DVT [5, 10].

However, the perioperative anticoagulated treatment of patients on antiplatelet therapy (aspirin, clopidogrel, and ticlopidine) is still a problem. Whether to stop or continue antiplatelet therapy is based on both cardiovascular and bleeding risks associated with surgery [2, 10-12]. In patients at a low risk for perioperative cardiovascular events, antiplatelet therapy should be discontinued 7 to 10 days before surgery [8]. In addition, in patients at a moderate or high risk for cardiovascular events, the American College of Chest Physicians recommends continuing aspirin therapy while holding clopidogrel 5 to 10 days before surgery [8, 9]. However, studies found that they may have greater perioperative blood loss [8, 9, 12].

Indobufen has been reported to have beneficial effects on blood coagulation and erythrocyte deformability [6, 13]. As a COX-1 inhibitor [14], indobufen has a definite antiplatelet effect. For perioperative patients on antiplatelet therapy, it is an ideal anticoagulant. However, currently there are few studies on the prevention and treatment of DVT by indobufen [3, 6, 10]. The effectiveness and safety of indobufen still needs to be additionally clarified. Thus, we have carried out this prospective, randomized, controlled study to further explore the anti-coagulation effectiveness and drug safety of indobufen in patients with total hip arthroplasty (THA).

Materials and methods

Study population

Patients with avascular necrosis of the femoral head (AVN), hip traumatic arthritis (OA), and developmental dysplasia of the hip (DDH) who had an indication for total hip arthroplasty (THA) and who were admitted to our hospital from January to December 2017, were analyzed in this study. The inclusion criteria were as follows: patients with AVN of ARCO [15] stage 3 to 4, or with DDH of Crowe [16] type 1 to 2; age > 18 and < 85 years, body mass index (BMI) > 18.5 and < 30; Caprini score ≥ 3 points and ≤ 15 points; a preoperatively complete compression ultrasound (CCUS) confirmed that no DVT existed. The main exclusion criteria were: history of thrombus disease; platelet < 100 × 10^9/L or history of thrombocytopenic purpura, aplastic anemia, hemophilia, and Mediterranean thrombocytopenia; disturbance of blood coagulation; hepatic dysfunction or renal dysfunction (glutamic pyruvic transaminase/glutamic-oxaloacetic transaminase increased by over 2.5-fold, creatinine clearance rate < 80 ml/min); gestation or lactation; serious heart disease, malignant hypertension and serious arrhythmia; active ulcer or history of gastrointestinal hemorrhage; cancer; use of anticoagulants (e.g. warfarin or heparin); allergic history of anticoagulants; serious heart failure (New York Heart Association class III to IV). The study was approved by the Chinese Ethics Committee of Registering Clinical Trials and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients prior to their participation in this study. This study is registered with the Chinese Clinical Trial Registry, number ChiCTR-IPR-17013008.

Study design

This study was a prospective, single-center, randomized controlled study. Eligible patients were randomized divided into two groups: the LMWH group and the INDO group. No anticoagulants were used preoperatively. Then, after standard preoperative examinations, each patient had a total hip arthroplasty. For each patient in the study, the operation was done by the same surgeon (Han Y). For the patients with

bilateral disease, the arthroplasty was performed one side first, then the other side in the same operation. The prevention of DVT was started at 6 hours postoperatively. These procedures included physical prophylaxis (active contraction of lower extremities in the first two days and standing-up/walking after two days) and drug prevention. For the LMWH group, low-molecular-weight heparin calcium (Changshan Pharmaceutical Company, Shijiazhuang, Hebei) was given by subcutaneous navel injection at a dose of 4100u per day. For the INDO group, indobufen (Huadong Pharmaceutical Company, Hangzhou, Zhejiang) was administered orally at a dose of 200 mg bid. The patients were discharged from hospital at 10 ± 3 days postoperatively. All the anticoagulants were continuously used no less than 35 days postoperatively. If DVT was detected in a patient, the anticoagulant dose was adjusted. The dose of LMWH was increased to 4100u bid and the dose of indobufen was increased to 300 mg bid respectively.

DVT evaluation

Pre- and post-operative DVTs were confirmed doing a complete compression ultrasound (CCUS) examination. The CCUS examinations were repeated within 3 days preoperatively, and on mean day 10 (3 days before or after), day 35 (3 days before or after) postoperatively. To ensure a high quality of standardized CCUS, all sonographers received CCUS training. Patient blood samples were also collected for laboratory analysis of hemoglobin and blood coagulation before the operation and on days 1 (only hemoglobin), 10 ± 3, and 35 ± 3, postoperatively.

Outcomes

The primary efficacy outcomes were morbidity and the severity of the DVTs. Secondary efficacy outcomes included the dominant (volume of drainage) and hidden hemorrhage (a fall in blood hemoglobin), a change in blood coagulation and an increase of D-dimmer concentration. The primary safety outcome was the incidence of major bleeding with onset no later than 2 days after the last dose of the study drug. Secondary safety measures included minor bleeding and the side effects of the drugs. Bleeding was considered major if it was fatal, affected a critical organ (retroperitoneal, intracranial, intraocular, or intraarticular), or was clinically overt and led to treatment cessation. A fall in blood hemoglobin over 20 g/L, or the transfusion of 2 or more units of packed red blood cells or whole blood was also defined as major bleeding. Other bleeding events were defined as minor bleeding.

Statistical analyses

Statistical analyses were performed using SPSS version 19.0 statistical software for Windows (IBM, Armonk, New York). Continuous variables were expressed as the mean ± SD and the categorical variables were expressed as frequencies. A Shapiro-Wilk test and a Levene test were used for testing the normality and homogeneity of variance. The parametric tests were applied when normality (and homogeneity of variance) assumptions are satisfied otherwise the equivalent non-parametric test was used. A Chi-square test was used for comparing the frequencies. Multivariable logistic regression analyses were used to detect the independent factors affecting the outcomes. A *P* value less than 0.05 was considered to be significant.

Results

General information of participants

A total of 225 patients were initially included in this study. 5 patients quit the study for personal reasons and 220 patients received the THA operation. During the follow-up period, 4 patients were lost due to contact alteration. Therefore, there were 216 patients available, and the related data were collected for the data analysis. The general information of two groups is shown in **Table 1**.

Primary efficacy outcomes

50 (23.15%) patients developed DVTs. 41 patients were found to have DVTs at 10 days postoperatively and 9 patients were found at 35 days. In the LWMH group, 28 patients had DVTs, including 21 patients with DVTs in their intermuscular veins, 5 patients with DVTs in their peroneal and posterior tibial veins, 1 patient with DVTs in his or her popliteal veins, and 1 patient with DVTs in his or her femoral veins. In the INDO group, 22 patients had DVTs, including 19 patients with DVTs in their intermuscular veins, 3 patients with DVTs in their

Table 1. General information of both groups

	INDO (n = 110)	LMWH (n = 106)	*P* value
Gender (male:female)	65:45	66:40	0.633
Side (unilateral/bilateral)	89:21	93:13	0.168
Age (years)	52.66 ± 13.51	52.73 ± 12.29	0.955
Body mass index	24.93 ± 2.74	24.45 ± 3.18	0.392
Operation time (min)	121.75 ± 48.13	113.83 ± 38.60	0.550
Blood loss intraoperation (ml)	504.56 ± 327.68	385.76 ± 12.29	0.006

INDO, indobufen group; LMWH, low molecular weight heparin group.

Table 2. Morbidity of deep vein thrombosis of both groups

	INDO (n = 110)	LMWH (n = 106)
Normal	88 (80.0%)	78 (73.6%)
DVT	22 (20.0%)	28 (26.4%)
Intermuscular veins	19 (17.3%)	21 (19.8%)
Peroneal and posterior tibial veins	3 (2.7%)	5 (4.7%)
Popliteal veins	0	1 (0.9%)
Femoral veins	0	1 (0.9%)
χ^2	3.908 (1.249)*	
P value	0.536 (0.264)*	

INDO, indobufen group; LMWH, low molecular weight heparin group; DVT, deep vein thrombosis. *χ^2 and *P* value between two groups in total DVTs.

peroneal and posterior tibial veins, and no patients had DVTs in their popliteal veins or in their femoral veins. The morbidity and severity showed no statistical differences between the two groups (**Table 2**). In addition, after increasing the dose of indobufen to 600 mg/day, 7/18 patients were found to have a thrombotic recanalization or disappearance at 35 days. For the LMWH group, 17/23 patients were found to have a thrombotic recanalization or disappearance after the dose had been increased.

Secondary efficacy outcomes

The volume of drainage was 671.62 ± 273.23 ml in the first two days postoperatively in group LWMH, which was 818.82 ± 346.22 ml in the INDO group. The volume of drainage in the INDO group was significantly higher than in the LWMH group LWMH (P = 0.001). A fall in blood hemoglobin within the first 10 days postoperatively was 8.25 ± 5.35 g/L in the LWMH group and 9.63 ± 6.23 g/L in the INDO group respectively, with no statistical difference (P = 0.136). D-dimer was increased obviously at 10 days and 35 days postoperatively in both groups. The D-dimer in the INDO group was significantly higher than it was in the LWMH group at 35 days postoperatively. Other laboratory analyses of blood coagulation showed no statistical differences (**Table 3** and **Figure 1**).

Safety outcomes

In this study, no major bleeding event occurred in either group. In the LMWH group, there was 1 patient with coagulation system complications (ecchymosis), 1 patient with other complications (erythra). In the INDO group, there were 3 patients with digestive complications (nausea, vomiting, abdominal pain and distention), but no other complication was found. The morbidity and classification showed no statistical differences between the two groups (χ^2 = 4.970, P = 0.174).

Risk factor for DVTs

In the multivariable logistic regression analysis, age, BMI, and the volume of intraoperational bleeding were the independent risk factors associated with DVTs (**Table 4**). The multivariable regression analysis showed the grouping had no effect on the onset of DVTs.

Discussion

In this prospective, randomized, controlled study, the total morbidity from DVTs was 23.15%. Among them, about 96% (48/50) of the DVTs were distal from the knee level. This indicated that the prevention of DVTs in this study was generally acceptable [5]. In addition, no PE or major bleeding events happened. The efficacy of indobufen in the treatment of cerebral, peripheral and coronary vascular disease is already well established [2, 6, 13]. In this study, the morbidities of DVTs in both groups were similar. This suggested that indobufen had an equivalent effect compared to LMWH on the prevention of DVTs. The later one was

Table 3. Laboratory analysis of blood coagulation of both groups

		INDO (n = 110)	LMWH (n = 106)	F	p
PT (s)	Pre-operation	11.31 ± 0.71	11.11 ± 0.64		
	10 days post-operation	12.08 ± 2.50	11.72 ± 0.80	6.536*	0.012*
	35 days post-operation	11.71 ± 1.26	11.41 ± 0.73		
	F	15.847*		0.229#	
	p	< 0.001*		0.731#	
APTT (s)	Pre-operation	30.39 ± 3.62	30.31 ± 3.65		
	10 days post-operation	29.43 ± 3.55	29.77 ± 2.85	0.351*	0.555*
	35 days post-operation	31.10 ± 4.13	30.16 ± 4.57		
	F	7.380*		3.194#	
	p	0.001*		0.047#	
INR	Pre-operation	1.03 ± 0.16	1.02 ± 0.19		
	10 days post-operation	1.16 ± 0.37	1.12 ± 0.29	3.707*	0.057*
	35 days post-operation	1.12 ± 0.28	1.03 ± 0.14		
	F	10.486*		1.318#	
	p	< 0.001*		0.269#	
TT (s)	Pre-operation	14.79 ± 1.24	15.03 ± 1.05		
	10 days post-operation	13.86 ± 1.31	14.19 ± 1.79	1.226*	0.271*
	35 days post-operation	14.00 ± 1.43	13.89 ± 1.64		
	F	32.664*		1.468#	
	p	< 0.001*		0.233#	
D-dimer (mg/L)	Pre-operation	0.31 ± 0.39	0.24 ± 0.27		
	10 days post-operation	1.66 ± 0.98	1.43 ± 0.76	15.251*	< 0.001*
	35 days post-operation	0.93 ± 0.80	0.54 ± 0.29		
	F	250.181*		3.110#	
	p	< 0.001*		0.061#	

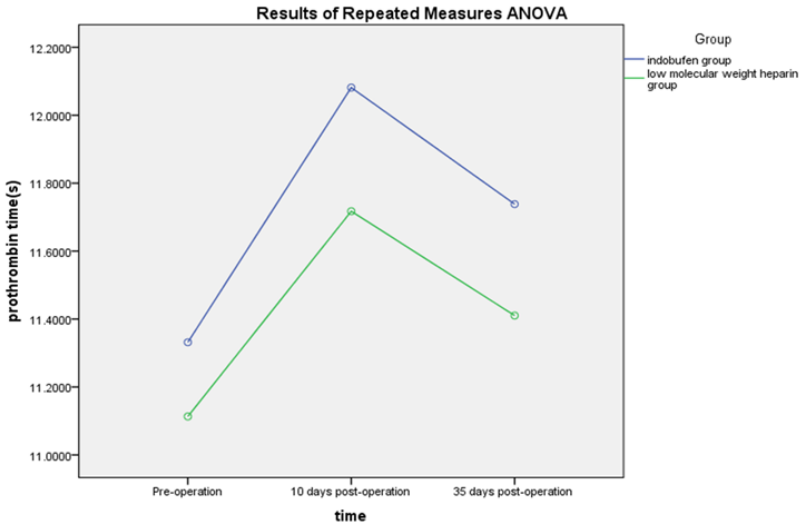
INDO, indobufen group; LMWH, low molecular weight heparin group; PT, prothrombin time; APTT, activated partial prothrombin time; INR, international normalized ratio; TT, thrombin time. *F statistic and *P* value of main effect; #F statistic and *P* value of crossover effect.

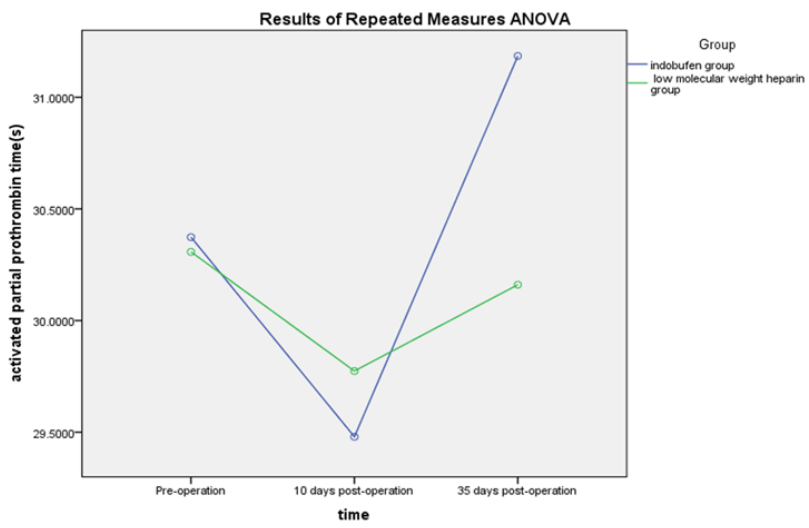
considered as the "gold standard" drug [3, 4, 14, 17]. Because LMWH was associated with fewer deaths [18], less major hemorrhaging [7], and lower rates of recurrent DVTs [11, 19], no laboratory monitoring is necessary [19]. As in our study, Borghi [13] also found that indobufen has an equivalent antithrombosis effect compared to LMWH, and it is superior to UFH. Montebugnoli [20] et al. had also drawn a similar conclusion that indobufen had a certain effect on the prevention of DVTs in orthopedic surgery. All these findings confirm the effectiveness of indobufen in the prevention of DVTs in patients with primary THA.

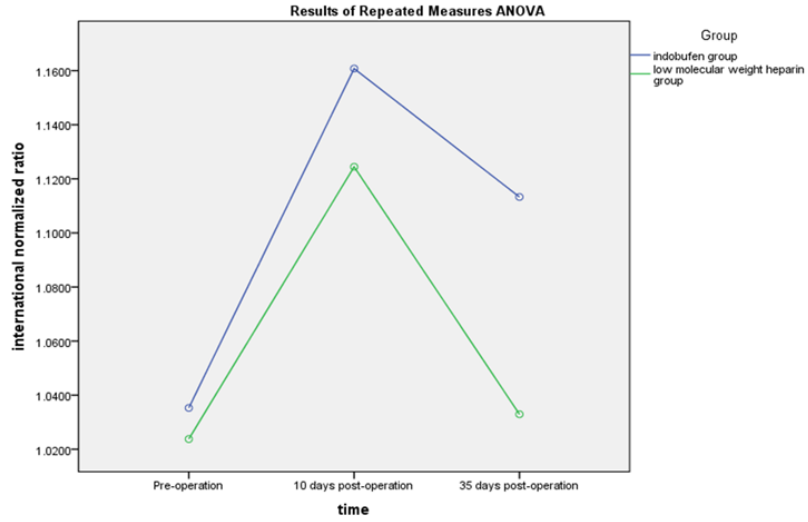
In the multivariable logistic regression analysis, age, BMI and volume of intraoperational bleeding were the independent risk factors associated with DVTs. But the group of patients did not have a significant risk factor associated with DVTs. This also indicates that the effect on the prevention of DVTs was similar for both indobufen and LMWH.

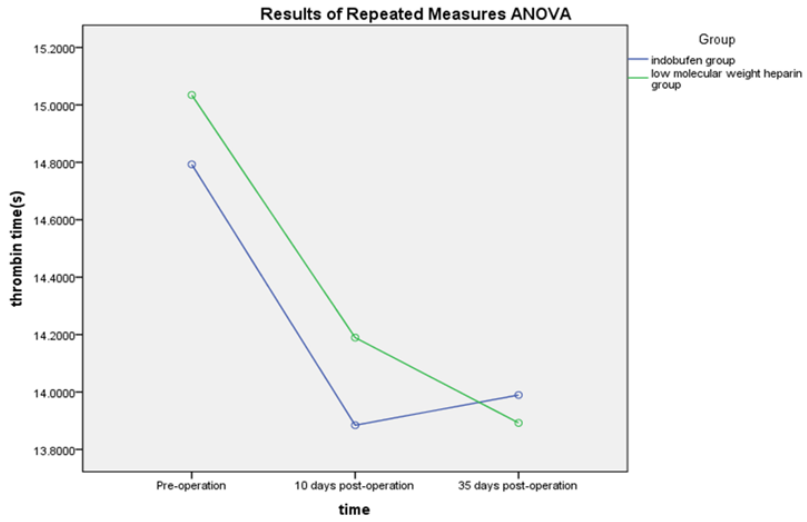
Another finding in this study was that for some of the patients who developed DVTs, thrombotic recanalization or disappearance were found after we increased the dose of indobufen to 600 mg/day. This suggests that indobufen has a potential therapeutic effect on DVTs. Furthermore, it indirectly indicates that indobufen has an anticoagulant effect.

Another key point for the anti-thrombosis drugs was the incidence of bleeding events [10]. As we all know, anticoagulants and bleeding were the main contradictions in the clinical use of the anti-thrombosis drugs, especially in the perioperative period [5, 13, 18]. In this study, the evaluations of bleeding were divided into two parts: dominant hemorrhage and hidden hemorrhage. Dominant hemorrhage was evalu-


Results of Repeated Measures ANOVA
prothrombin time(s)
12.2000
12.0000
11.8000
11.6000
11.4000
11.2000
11.0000
Pre-operation
10 days post-operation
35 days post-operation
time
Group
indobufen group
low molecular weight heparin group


Results of Repeated Measures ANOVA
activated partial prothrombin time(s)
31.0000
30.5000
30.0000
29.5000
Pre-operation
10 days post-operation
35 days post-operation
time
Group
indobufen group
low molecular weight heparin group


Results of Repeated Measures ANOVA
international normalized ratio
1.1600
1.1400
1.1200
1.1000
1.0800
1.0600
1.0400
1.0200
Pre-operation
10 days post-operation
35 days post-operation
time
Group
indobufen group
low molecular weight heparin group


Results of Repeated Measures ANOVA
thrombin time(s)
15.2000
15.0000
14.8000
14.6000
14.4000
14.2000
14.0000
13.8000
Pre-operation
10 days post-operation
35 days post-operation
time
Group
indobufen group
low molecular weight heparin group

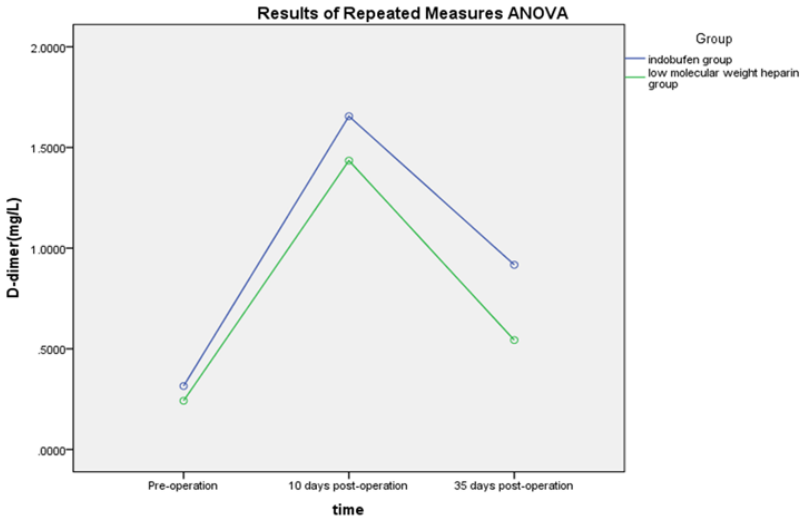


Figure 1. Results of repeated measures ANOVA analysis. The blue lines show the level of different coagulation index in group indobufen. The green lines show the level of different coagulation index in group low molecular weight heparin.

Table 4. Risk factors of deep vein thrombosis

	P	OR	OR 95% CI
Age	0.032		
< 45 years	Reference		
45-60 years	0.023	3.472	1.188-10.149
> 60 years	0.010	4.264	1.422-12.783
Body mass index	0.024		
24-28	Reference		
< 24	0.044	2.159	1.022-4.558
> 28	0.012	3.479	1.322-9.155
Operation time (min)	0.084	0.991	0.980-1.001
Operation bleeding (ml)	0.029	1.002	1.000-1.003

OR, odd ratio; CI, confidence interval.

ated by the volume of postoperative drainage. However, because it is affected by position, the depth of the drainage tube, and by the bleeding at the incision point, drainage might not reflect the hemorrhage accurately [1]. In this study, the volume of drainage was higher in the INDO group, and this may because there were more bilateral patients than in the LMWH group. But it also suggests that for patients with indobufen, the risk of bleeding may be potentially higher than in patients with LWMH. In addition, we had investigated falls in blood hemoglobin to reflect hidden hemorrhaging. The results showed no significant difference between two groups. This suggests that even with additional antiplatelet function, indobufen apparently did not increase the perioperative period hemorrhaging. Furthermore, there was no major bleeding event in this study, indicating that it is a relatively safe drug for the patients who received a THA operation for the prevention of DVTs.

Although CCUS was the major diagnostic method of DVTs [5], blood coagulation analysis and D-dimer concentration were of great clinical significance and value [21]. D-dimer had a relatively high sensibility in DVT diagnosis and might help detect the subclinical DVTs [6]. It became elevated before significant DVT formation [22]. In this study, D-dimer concentration increased at 7 days postoperatively, and still exceeded the normal value at 35 days. The D-dimer concentration of the INDO group was higher than the LMWH group at 35 days. But we do not find any clinical significance here. In addition, the blood coagulation analysis showed few changes in either group.

As a COX-1 inhibitor, the side effects of indobufen mainly included digestive complications such as nausea, vomiting, abdominal pain and distention [13]. By comparison, the side effects of LMWH were different in this study. Erythra was also found and considered as an indication of allergy. But no significant difference in morbidity was found.

The limitations of this study were as follows. First, the sample size was relatively small. Second, the follow-up time was short, making us unable to determine the long-term morbidity of DVTs. Furthermore, as it was not a double-blind trial, subjective factors may have influenced the results of this study. In addition, a single-center study might not exclude the unknown influencing factors of DVTs.

Conclusion

Compared with LMWH, indobufen had a similar effect on the prevention of DVTs in patients with primary THA. The morbidity and severity showed no significant differences between the two groups. In addition, no major bleeding event occurred in this study. As a COX-1 inhibitor, indobufen may be more appropriate for perioperative period patients on antiplatelet therapy.

Disclosure of conflict of interest

None.

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