Early Postoperative Bleeding in Polytrauma Patients Treated with Fondaparinux: Literature Review and Institutional Experience

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Abstract: Surgery for pelvic or acetabular fractures carries a high risk of deep-vein thrombosis (DVT). Reports indicate that fondaparinux is a more effective thromboprophylactic agent than low molecular weight heparin (LMWH) after major orthopaedic surgery. The safety and efficacy of fondaparinux was evaluated in a new protocol used for DVT prophylaxis. One hundred and twenty seven patients with pelvic or acetabular fractures received either fondaparinux or enoxaparin and were analysed in a historical non-concurrent study. Specific review points included clinical deep-vein thrombosis (DVT) or pulmonary embolism (PE) and evidence of adverse effects such as bleeding or allergic reactions. Two patients that received enoxaparin were found to have a DVT and one patient had a PE. There was no documented DVT or PE in patients that received fondaparinux. The mean number of units of blood transfused postoperatively was higher in the enoxaparin group; however, multivariate regression modelling demonstrated no significant difference between the groups. The most current large randomised controlled studies investigating the administration of fondaparinux following joint arthroplasty or hip fracture surgery, have demonstrated a slight increase or a similar number of bleeding events in patients treated with fondaparinux when compared to those treated with enoxaparin. The current report supports that fondaparinux, in patients with pelvic and acetabular fractures, can be equally effective as enoxaparin and not associated with adverse bleeding events.

Keywords: Pelvis, acetabulum, fracture, deep-vein thrombosis, anticoagulant, enoxaparin, fondaparinux.

INTRODUCTION

Major lower-limb orthopaedic surgery results in a hypercoagulable state, which coupled with long periods of postoperative immobility, places patients at an increased risk of thrombotic complications [1-3]. The incidence of DVT after pelvic trauma has been reported at between 35 and 60%, dependent upon diagnostic techniques employed [2, 3]. Pulmonary embolism (PE), the most significant potential thrombotic complication, has a reported incidence of 2–10% with a mortality of 0.5–2% [1, 2]. Standard thromboprophylaxis after hip or knee arthroplasty consists of low molecular weight heparin in many centres [4, 5]. This has the advantage of a fixed, well defined once daily dosing regimen administered by subcutaneous injection. Despite this, DVT remains a relatively frequent complication after such procedures and the need for improved thromboprophylaxis is well recognised [3, 6].

The pentasaccharide, fondaparinux, has been approved for use in major orthopaedic surgery, with large randomised controlled trials demonstrating significant decreases in the incidence of DVT and PE after hip or knee surgery when compared to enoxaparin [7-12]. Studies suggest an increased effectiveness in comparison with LMWH, this has been attributed to improved pharmacologic characteristics and rapid selective inhibition of factor Xa [7-9, 11, 13-15]. This has however been tempered by higher rates of major bleeding associated with its use in some studies [5, 7], though other series refute this [8, 11, 13]. These seemingly contradictory results may reflect the different administration regimens used as well as differences in the primary surgical condition between studies [10, 16].

Patients with high energy skeletal trauma have perhaps the greatest risk of thromboembolic complication [3] and there is currently no available literature comparing LMWH and fondaparinux in patients with pelvic or acetabular fractures. Furthermore, the optimal approach in the management of thromboembolic risk in this group of patients is unclear, with aggressive prophylaxis employed in most cases [2].

Our level I trauma centre deals with relatively large numbers of patients with pelvic and acetabular injury. For a period beginning in November 2004, fondaparinux was used as routine postoperative thromboprophylaxis for such patients in place of enoxaparin. We therefore present the findings of a non-concurrent historical comparison study comparing the safety and effectiveness of fondaparinux with enoxaparin.

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PATIENTS AND METHODS

This study has been approved by the medical ethics committee of our institution. Data was collected retrospectively from a sample of patients that required operations for acetabular fractures (AF), pelvic fractures (PF), or a combination of acetabular and pelvic fractures (CF) between February 2005 until June 2006 (16 months) and received enoxaparin for thromboprophylaxis. From July 2006 until November 2007 (16 months), data was collected prospectively from patients that required operations for AF, PF or CF injuries that received fondaparinux for postoperative thromboprophylaxis. Factors that could influence bleeding were recorded including the Injury Severity Score (ISS); time from injury to operation (days) and the duration of the operation (minutes). Haemoglobin values pre-and postoperatively and the number of units of blood transfused for each patient pre-, peri-, and postoperatively were also recorded. Standard unit policy to consider transfusion in patients with a postoperative haemoglobin of less than 8 grams per deciliter (g/dl) remained unchanged throughout both study periods.

Patients in both groups received enoxaparin 40mg at 1800 hours on the day of admission, provided the patient was haemodynamically stable (assessed by looking at trends in pulse, mean arterial pressure (>60 mmHg) and urine output > ½ ml/kg/hour) and no contraindications existed. Enoxaparin was discontinued 12 hours prior to surgery and, in the enoxaparin group, recommenced at 6 hours following surgery and then given once daily until discharge. This was replaced in the fondaparinux group by 2.5mg administered 6 hours postoperatively and continued once daily until discharge. Patients in both groups were discharged on Aspirin 75mg once daily for two months.

Contraindications for administration, according to the manufacturers, included known hypersensitivity to heparin, LMWH or pentasaccharides or any their excipients; acute clinically significant bleeding; acute bacterial endocarditis; severe renal impairment (GFR<30ml/min); any medical conditions in which anticoagulation is contraindicated (current ulceration; haemorrhagic stroke; brain, spinal or ophthalmological surgery within the previous 3 months). During the study periods, no patients were excluded for the above reasons.

Outcome Measures

The primary outcome measure in this study was clinically relevant thromboembolic event. Patients were reviewed daily as an inpatient for clinical evidence of a DVT or PE. Suspected DVT was assessed routinely with duplex ultrasound according to our hospital protocol if there was a recorded Wells score of ≥ 7 [17]. Suspected PE was investigated with CT-pulmonary angiography. Adverse effects in all patients such as bleeding, thrombocytopenia, deranged clotting [assessed using the coagulation parameters: thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (aPTT)], or allergic reactions were also documented as secondary outcome measures.

Statistical Analysis

By using STATA version 10 for Windows XP, a multivariable regression model was utilised to analyse the influence of factors such as age, sex, ISS, time from injury to operation, operation duration and the method of anticoagulation on the number of units transfused postoperatively. Student's unpaired t-test was used to determine if differences in the average pre- and postoperative haemoglobin values and the number of units transfused were significant between groups.

RESULTS

Fifty-nine patients received fondaparinux and 68 received enoxaparin. The two treatment groups were comparable for age, sex, type of injury, average ISS and duration of therapy (Table **1**). The mean duration of the inpatient therapy was 19.5 days (SD: 12.3 days) in enoxaparin and 8.3 days (SD: 8.7 days) in the fondaparinux group (p=0.3; student's unpaired t-test). Two patients that received enoxaparin were found to have a DVT and one patient had a PE. There was no DVT or PE in patients that received fondaparinux.

Blood Loss and Requirement for Blood Transfusion

In those treated with fondaparinux, 20 out of 59 (34%) required a blood transfusion postoperatively compared with 27 out of 68 (40%) in those treated with enoxaparin. Analysis of pre- and postoperative differences in haemoglobin values revealed no significant difference between those treated with enoxaparin (-1.6 ± 1.8 g/dl (mean ± SD; n=61)) and those receiving fondaparinux (-1.3 ± 1.6 g/dl (mean ± SD; n=59)) (p=0.1; student's unpaired t-test). Similarly, there was no significant difference in the pre- and postoperative number of units transfused between groups (fondaparinux group, 0.4 ± 1.5 units compared to 0.2 ± 1.7 units for enoxaparin (p=0.5; student's unpaired t-test)). No adverse effects such as, thrombocytopenia, deranged clotting or allergic reactions were found in either group. After adjusting for other factors, patients on fondaparinux lost 0.3 units less on average and there was no statistical difference in the method of anticoagulation with regard to blood loss. Males lost 0.6 units less and a longer operation was associated with more blood required postoperatively. Patients with pelvic fractures required on average 0.6 units more than those with acetabular fractures. A longer delay before the operation was associated with a reduced number of units transfused. A higher ISS was associated with a greater number of units transfused postoperatively; this was calculated as 0.03 units per point of ISS (Fig. **1**, Table **2**).

DISCUSSION

As far as we are aware, this is the first study to evaluate the safety and effectiveness of fondaparinux for thromboprophylaxis in pelvic and acetabular trauma. The results suggest that fondaparinux is safe as it does not appear to be associated with increased risk of bleeding or adverse effects compared to enoxaparin. The most commonly reported adverse event associated with fondaparinux is clinically significant bleeding [18]. Recently, the FDA has revised the safety label for fondaparinux to warn of the potential for elevation of the aPTT in association with an increase in bleeding events. However, the coagulation parameters aPTT and PT time have been considered as relatively insensitive markers of fondaparinux activity [19]. There have also been reports of

Table 1. Baseline Data

	Enoxaparin			Fondaparinux		
	AF	**PF**	**CF**	**AF**	**PF**	**CF**
Mean age (SD) years	39.7 (14.7)	36.0 (17.1)	28.0 (9.8)	43.0 (16.7)	40.5 (13.4)	39.7 (20.1)
Total mean Age ± (SD)	37.8 ± (15.5)			41.2 ± (16.3)		
p value	0.2					
Sex: Male	34	17	4	22	15	9
Female	6	7	0	4	5	4
Total patients	40	24	4	26	20	13
	68			59		
Male *vs.* Female (Enoxaparin *vs*. Fondaparinux; *p* value; Fisher's exact test)				*p*=1.0	*p*=1.0	*p*=0.5
Total Average ISS ± (SD)	19.3 ± (13.4)			17.5 ± (9.0)		
p value	0.4					
Mean pre-op units	1.1 ± (3.3)			0.9 ± (1.5)		
Mean pre-op Hb ± (SD)	11.8 ± (1.7)			11.5 ± (1.9)		
Mean post-op Hb ± (SD)	10.2 ± (1.5)			10.2 ± (1.4)		
Mean Hb difference ± (SD)	1.6 ± (1.8)			1.3 ± (1.6)		
p value	0.4					
Mean peri-op units ± (SD)	0.9 (1.6)			0.3 (0.6)		
Mean post-op units ± (SD)	1.1 (1.6)			0.7 (1.4)		
Units tranfused difference ± (SD)	0.2 (1.7)			0.4 (1.5)		
p value	0.5					

Abbreviations: AF: acetabular fracture, PF: pelvic fracture, CF: combination acetabular and pelvic fracture.

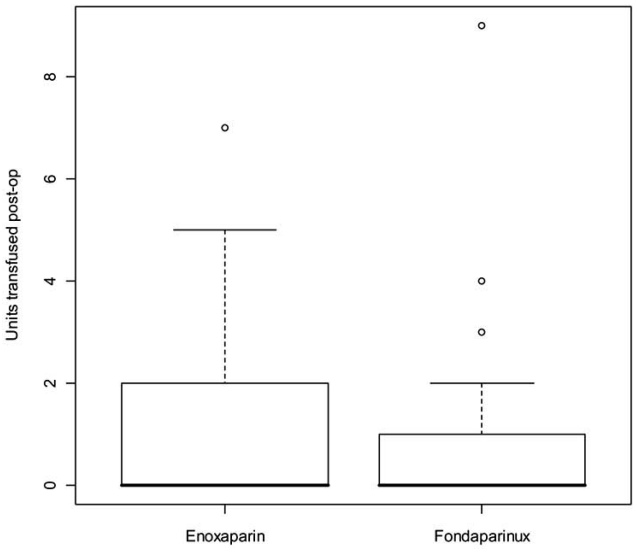

Fig. (1). Boxplot demonstrating the degree of spread and skewness in the postoperative number of units transfused accounted for by the anticoagulant given. The median value lies at 0 units in both groups. The bottom and top of the box are the 25th and 75th quartiles. The whiskers denote the range of the postoperative number of units transfused. Points beyond the whiskers denote patients with higher blood loss than expected.

pathologic fall in platelet concentration resembling heparin induced thrombocytopenia [19]. Current recommendations suggest that if the platelet count falls below 100,000/mm^3 or there is a change in aPTT or PT time then fondaparinux should be discontinued [19]. In this study we found no adverse effects associated with fondaparinux such as rash and pruritis, or more serious effects like thrombocytopenia, deranged clotting or allergic reactions but this is probably attributable to the relatively small numbers of patients included [18]. Pelvic and acetabular fractures are uncommon but very serious injuries treated in level I trauma centres, therefore very large numbers of patients available to study are very difficult to obtain unless a multicentre study is conducted.

The most current randomised controlled studies investigating the administration of fondaparinux following joint arthroplasty or hip fracture surgery have demonstrated either a slight increase or a similar number of bleeding events in patients treated with fondaparinux when compared to those treated with enoxaparin [8, 20, 21]. In a study by Erikkson *et al.*, 2001 (PENTIFRA) [8], 1711 patients with hip fractures were randomised to receive either fondaparinux 2.5mg initiated 6 ± 2h postoperatively or enoxaparin 40mg initiated 12 ± 2h preoperatively for 1 week. By day 11, the incidence of DVT was 8.3% *vs.* 19.1% (p<0.001). The incidence of major bleeding was 2.2% in both groups (p=1.0) and minor bleeding occurred more frequently in the fondaparinux group

Table 2. Multiple Regression of the Postoperative Blood Loss in Units on Method of Anticoagulation, Sex, Operation Duration (Mins), Pelvic or Acetabular Fracture, Time between Injury and Surgery (days) and Injury Severity Score. Patients on Fondaparinux Lost 0.3 Units Less on Average after Adjusting for all other Factors and there is no Statistical difference in the Method of Anticoagulation with Regard to Blood Loss. Males Lost 0.6 Units less than Females. A Longer Operation was Associated with a Greater Requirement of Blood Required Postoperatively. Patients with Pelvic Fractures Required 0.6 Units more than those that Sustained Acetabular Fractures. A Longer Delay before the Operation was Associated with a Reduced Number of Units Transfused Postoperatively. A Higher ISS was Associated with an Increased Number of Units Required Postoperatively, 0.03 Units per Point of ISS. Total Number of Observations = 119; Prob > F = 0.0007; R-squared = 0.2; Adj R-squared = 0.2

Number of Units Transfused Postoperatively	Regression Coefficient	Standard Error	*t* Value	*p* Value	95% Confidence Interval
Fondaparinux	- 0.3	0.3	-1.2	0.2	-0.9 – 0.2
Male sex	- 0.6	0.3	- 1.8	0.1	-1.3 – 0.04
Operation duration (mins)	0.002	0.001	1.82	0.07	-0.0002 – 0.004
Pelvic fracture	0.6	0.3	2.0	0.05	-0.004 – 1.2
Acetabular fracture	- 0.08	0.4	-0.2	0.9	-0.9 – 0.8
Time between injury and operation (days)	- 0.04	0.01	-2.4	0.02	-0.7 – -0.006
ISS	0.03	0.01	2.2	0.03	0.003 – 0.05

Table 3. Randomised Controlled Trials Investigating the Degree of Bleeding in Patients Treated with Fondaparinux Following Major Orthopaedic Surgery

Author - Year	Sample	Thromboprophylaxis Regimens	Safety Outcome Endpoint	Incidence	Concerns
Eriksson *et al.* 2001 [8] PENTIFRA	1711 Hip fracture patients (99 centres, 21 countries)	FS *vs.* ES for 7 days (2.5mg *vs.* 40mg)	Major bleeding – 11th day pop Minor bleeding – 49th day pop	2.2% *vs.* 2.2% (p=1.0) 4.1% *vs.* 2.1% (p=0.02)	Pre-operative cover of the FS group Timing of first dose of FS
Turpie e*t al.* 2002 [20] Meta-analysis of 4 randomised double-blind trials	Comparison of EPHESUS [9] (elective hip surgery n = 2309); PENTATHLON [11] (total hip reconstruction surgery n=2275); PENTAMAKS [7] (major knee surgery, n=1049); and PENTHIFRA [8] (hip fracture surgery, n=1711)	FS (n = 3668) *vs.* ES (n =3676)	Overall bleeding events	2.7% *vs.* 1.7% (p=0.008)	Post hoc analysis identified significant correlation between incidence of bleeding and timing of FS injection (between 3 and 9h pop; p=0.008). 23% of this meta-analysis were trauma patients.
Eriksson *et al.* 2003 [21] PENTI-FRA-PLUS	737 Hip fracture patients (57 centres, 16 countries)	FS *vs.* Placebo from week 2 to 4 (2.5mg)	Major bleeding – 4th week pop Minor bleeding – 4th week pop	2.4% *vs.* 0.6% (p=0.06) 1.5% *vs.* 0.6%	Pre-operative cover of the FS group Not compared with another thromboprophylactic agent for the same time period. Timing of first dose of FS

FS: fondaparinux sodium; ES: enoxaparin sodium; pop: postoperative.

(4.1% *vs.* 2.1%; p=0.02). In a meta-analysis of 4 randomised double-blind trials including a considerable number of trauma patients (23%), Turpie *et al.*, 2002 [20] found a significant difference in overall bleeding events between fondaparinux and enoxaparin treated groups (2.7% *vs.* 1.7%; p=0.008). An increased incidence of bleeding was associated with the timing of fondaparinux administration between 3 and 9h postoperatively (p=0.008). In a further study by Eriksson *et al.*, 2003 (PENTIFRA-PLUS) [21], 737 hip fracture patients received fondaparinux as prophylaxis for 1 week following surgery. Patients were then randomised to receive either fondaparinux for a further 3 weeks or placebo.

Fondaparinux was found to be associated with a greater number of major bleeding events than placebo at the 4 week time point (2.4% *vs.* 0.6%; p=0.06). Table **3** illustrates randomised controlled trials investigating the degree of bleeding following fondaparinux administration. Parameters such as the bleeding index [calculated as the number of units of packed red blood cells or whole blood transfused + (preoperative minus postoperative haemoglobin in g/dl)] were also found to be increased in those treated with fondaparinux [21]. The value of this measurement however been called into question as it may not truly reflect increased incidence of fatal bleeding, critical organ bleeding or bleeding leading to reoperation [9, 18, 22]. Therefore in the current study, the drop in haemoglobin and the number of units transfused were used as separate indicators of bleeding rather than calculating the bleeding index. We found no significant difference in the postoperative fall in haemoglobin concentration between the two treatment groups when examining the raw data (Table **1**). After adjusting for other factors including demographics, time to surgery, duration of the procedure, type and severity of injury, we found that patients with pelvic fractures required on average 0.6 units more than those with acetabular fractures (p=0.05); a longer delay before the operation was associated with a reduced number of units transfused (p=0.02); and a higher ISS was also associated with a greater number of units transfused postoperatively (p=0.03) (Fig. **1**, Table **2**).

Adherence to the recommended time of first administration, 6 hours post wound closure, is considered to be important as earlier administration may result in an increased risk of bleeding [9, 18, 23]. When administered at least 6 hours (and up to 12 hours) postoperatively, its greater efficacy over enoxaparin may also be maintained [23]. Studies have indicated that extended prophylaxis with fondaparinux following major orthopaedic surgery is associated with increased effectiveness, possibly more significant than enoxaparin [21, 24]. In the current study, all pelvic and acetabular fracture patients were administered fondaparinux 6 hours post wound closure and during the period of inpatient stay. The usual duration of therapy with fondaparinux in the literature is 5–9 days and extended prophylaxis of 28 days is recommended in hip fracture surgery [18]. Evidence suggests that fondaparinux is a safe and cost-effective alternative to enoxaparin in elective hip and knee arthroplasty [18]. Furthermore, the literature supports its use for extended prophylaxis to reduce both symptomatic and venography proven DVT in hip-fracture patients [8, 18, 23, 25].

Our data suggest that fondaparinux can also be considered as an alternative anticoagulant in pelvic and acetabular fracture patients. With the numbers available and the limitations of our study design we can not claim that fondaparinux is safer and more effective than enoxaparin, but bleeding was found to be related to other factors such as the type of injury, ISS, the time to surgery and not to the type of anticoagulant. The strengths of this study include the assessment of clinically relevant outcomes in a group of polytrauma patients at greater risk of bleeding and DVT and PE. Further randomised controlled studies with sufficient power are necessary to investigate the optimal duration of therapy and the risk of clinically relevant bleeding with extended prophylaxis in patients with pelvic and acetabular trauma.

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