Title

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Journal

Journal of Orthopaedics, 15(2)

ISSN

2589-9082

Authors

Lum, Zachary C

Monzon, Rene A

Bosque, Jose

et al.

Publication Date

2018-06-01

DOI

10.1016/j.jor.2018.03.003

Peer reviewed

Journal of Orthopaedics 15 (2018) 388–390

Contents lists available at ScienceDirect

Journal of Orthopaedics

journal homepage: www.elsevier.com/locate/jor

Effects of fondaparinux on wound drainage after total hip and knee arthroplasty

Zachary C. Lum*, Rene A. Monzon, Jose Bosque, Sheldon Coleman, Gavin C. Pereira, Paul E. Di Cesare

University of California: Davis Medical Center, Adult Reconstruction, Department of Orthopaedics, 4860 Y Street, Suite #3800, Sacramento, CA 95817, United States

ARTICLE INFO

Keywords:
Anticoagulation in arthroplasty
Wound drainage in total joint arthroplasty
Arixtra
Fondaparinux
Surgical site infections
Length of stay

ABSTRACT

Background: The purpose of this investigation was to determine the effects of fondaparinux on postoperative wound drainage, length of hospital stay (LOS) and rate of surgical site infection in total joint patients.
Methods: 117 patients undergoing total joint arthroplasty treated with fondaparinux for venous thromboembolism (VTE) prophylaxis were prospectively studied.
Results: The average time to a dry wound was 3.4 days, with an average LOS of 3.77 days. Perioperative complications included 2 cases each of superficial cellulitis, deep vein thrombosis, and pulmonary embolism; there were no cases of deep infection. Multi-variate analysis showed increased patient BMI increased LOS ($p = 0.0169$).
Conclusion: Fondaparinux is an effective drug for VTE prophylaxis in total joint arthroplasty with wound drainage and LOS comparable to historical controls of enoxaparin, warfarin, and rivaroxaban.

1. Introduction

Total joint arthroplasty (TJA) has significantly improved the pain and function of patients with degenerative joint diseases; however, it does not come without risks for morbidity and mortality.[1] Complications related to TJA include infection, aseptic loosening, dislocation, leg length discrepancy, neurovascular injury, and venous thromboembolism (VTE).[2–5]

The agents used for VTE prevention have been shown to be effective however, they can increase the risk of post-operative wound complications resulting in surgical site infections.[6,7] Prolonged wound drainage associated with anticoagulation following total hip (THA) or total knee arthroplasty (TKA) has been associated with increased post-operative morbidity.[8–10]

Fondaparinux (trade name Arixtra, GlaxoSmithKline, Middlesex, UK) is an anticoagulant medication chemically related to the low molecular weight heparins. Fondaparinux is a synthetic pentasaccharide Factor Xa inhibitor. Apart from the O-methyl group at the reducing end of the molecule, the identity and sequence of the five monomeric sugar units contained in fondaparinux is identical to a sequence of five monomeric sugar units that can be isolated after either chemical or enzymatic cleavage of the polymeric glycosaminoglycans, heparin and heparan sulfate (HS). Within heparin and heparan sulfate this monomeric sequence is a high affinity binding site for the anti-coagulant factor antithrombin III (ATIII). Binding of heparin/HS to ATIII has been shown to increase the anti-coagulant activity of antithrombin III 1000-fold. In contrast to heparin, fondaparinux does not inhibit thrombin. One potential advantage of fondaparinux over LMWH or unfractionated heparin is that the risk for heparin-induced thrombocytopenia (HIT) is substantially lower. Furthermore, there have been case reports of fondaparinux being used to anticoagulate patients with established HIT as it has no affinity to platelet factor 4 (PF-4). Fondaparinux is removed from the patient's serum by renal excretion, which precludes its use in patients with renal dysfunction. Fondaparinux is given subcutaneously daily. Unlike direct factor Xa inhibitors, it mediates its effects indirectly through antithrombin III, but unlike heparin, it is selective for factor Xa.

The purpose of this investigation was to determine the effects of fondaparinux on postoperative wound drainage after total hip and knee arthroplasty and secondary outcomes of hospital length of stay and surgical site infection rates.

2. Methods

All research herein was conducted in accordance with ethical standards in compliance with privacy guidelines and in accordance with our institution and independent institutional review board. All patients were considered for inclusion in the study that met inclusion

* Corresponding author.
E-mail address: zclum@ucdavis.edu (Z.C. Lum).

https://doi.org/10.1016/j.jor.2018.03.003
Received 9 February 2018; Accepted 16 March 2018
Available online 17 March 2018

criteria and data was collected as a non-randomized prospective cases series. All patients had signed informed consent to be included in the study. Patient were excluded that had who declined consent or for whom consent was not obtained, whose surgeries were performed at an ambulatory surgery center, who underwent simultaneous bilateral arthroplasty procedures, who underwent lateral unicompartmental, patellofemoral replacement, or revision of a previous hip or knee arthroplasty, who weighted < 50 kg, had severe renal impairment (CrCl < 30 ml/min), had a history of hypersensitivity to fondaparinux, had active significant bleeding, had bacterial endocarditis, had a history of GI ulceration in the last 6 months and/or had a history of diabetic retinopathy.

For TKA, a medial parapatellar arthrotomy was performed; for THA, a posterolateral approach was utilized for each operation. Patients were administered 2.5 mg of fondaparinux subcutaneously for VTE prophylaxis daily beginning 12–24 h postoperatively for 10 days. All patients also received a multimodal pain protocol including acetaminophen 500 mg every 4 h.

Primary outcomes were wound drainage; secondary outcomes were length of stay (LOS) and infection rates. Wound drainage was recorded according to Weiss et al 11 whereby they defined it as "fluid drainage that would significantly wet or soak at least a 2 × 2 centimeter area of gauze dressing from the surgical site. Simple spotting of dressings, small edges from ulceration or marginal necrosis did not classify as persistent drainage." Wound drainage was calculated by number of days until a dry wound. Photos of the dressing were obtained on each post-operative day, starting on the second post-operative day and calculated using NIH Image, to obtain accurate measurements of drainage area. Number of days in the hospital and incidence of wound infection were calculated.

Patient demographics (BMI, age, sex, height, weight) and perioperative variables (anesthesia type, surgeon, laterality, arthroplasty type, estimated blood loss (EBL), length of stay) were recorded and analyzed for other risk factors for wound drainage. Postoperative complications were recorded (DVT/VTE, hematoma, reoperation, infection).

The time to cessation of wound drainage of patient receiving Arixtra was statistically compared to standard therapies assuming a 16% difference between the longest draining standard prophylaxis (LMWH) and Arixtra to be significant. Given this assumption a power analysis revealed a sample size of 91 Arixtra patients in the proposed series to be able to detect to detect a significant difference with 80% power in drainage time between this trial therapy and the standards of care at our institution.

ANOVA with Bonferroni adjusted multiple comparisons was used to compare the differences in wound drainage (the number of days until a dry wound is achieved) and length of stay by DVT prophylaxis types. Logistic regression was used to model the log-odds of infection by prophylaxis type.

3. Results

From February 2013 to February 2014, 117 patients undergoing unilateral TKA or THA were prospectively enrolled and followed for 1 year during their preoperative and postoperative hospital course after signing informed consent. Perioperatively, the average time to a dry wound was 3.4 (1–10) days with fondaparinux as VTE prophylaxis. For THA patients, 22 patients had a dry dressing by postoperative day (POD) 4 with an average time to discharge at 3.31 days. 15 patients had wet dressings on POD 4 with an average discharge of 4.08 days. For TKA patients, 26 patients had a dry dressing by POD 4 with average discharge at 3.16 days. 11 patients in the TKA cohort had a wet dressing at POD 4, with average discharge at 5.28 days. The average LOS of 3.77 (2–12) days.

Perioperative complications included 2 cases each of superficial cellulitis (2.8%), DVT (2.8%), and PE (2.8%). No patient developed a deep infection. One patient (1.4%) required reoperation for hematoma. One patient had to stop fondaparinux therapy due to an allergic reaction. Upon multi-variate analysis, increased patient BMI showed significantly increased LOS ($p = 0.0169$). There was no difference in wound drainage with regards to sex, type of surgery nor estimated blood loss ($p = 0.2724$; 0.0779; 0.91, respectively)

4. Discussion

Prolonged postoperative wound drainage following total joint arthroplasty is clinically relevant due to the associated risk for VTE events (should the anticoagulant be discontinued), length of hospital stays, and infection.[6] One of the most important variables in postoperative care is the selection and management of appropriate thromboprophylaxis during the postoperative course.[12] Anticoagulants are commonly used in postoperative TJA to prevent VTEs, however, there is a delicate balance between VTE prevention and wound complications. Results from this investigation show that Fondaparinux is effective for VTE prophylaxis in total joint arthroplasty with an amount of wound drainage comparable to historical controls of enoxaparin, warfarin, and rivaroxaban.

Previous studies have reported that patients with prolonged wound drainage after total hip or total knee arthroplasty have a significantly longer hospital stay.[6] This suggests that prolonged wound drainage has a positive correlation to length of stay, and therefore the length of stay can be used as a surrogate for wound drainage to compare fondaparinux to other anticoagulant agents. Gutowski et al, reported that 1213 patients undergoing TJA received aspirin for VTE prophylaxis and had an average length of stay of 2.6 days.[13] This same study also reported that 4159 patients undergoing TJA receiving warfarin for VTE prophylaxis had an average length of stay of 3.7 days.[13] In a similar study, Herschman et al reported that patients undergoing TKA's treated with enoxaparin, or rivaroxaban as prophylaxis had an average length of stay of 5 days, and 4.1 days, respectively.[14] Results from this investigation suggests that fondaparinux may have a lower length of hospital stay when compared to enoxaparin and rivaroxaban, an increased length of stay when compared to aspirin, and a comparable length of stay to warfarin, as the average length of stay was 3.77 days.

Wound drainage has also been associated with an increased risk of infection in the setting of TJA.[15] In a study determining the factors associated with prolonged wound drainage, length of hospital stay and, rate of wound infections by Patel et al 1211 patients undergoing TJAs, and 1226 patients undergoing TKAs were treated with either warfarin, enoxaparin, or aspirin as prophylaxis for VTE's.[6] Using the Weiss method for calculating wound drainage, those authors noted that at five days postoperatively, the surgical wound was dry in 87% of the patients receiving warfarin, in 83% of those treated with aspirin and mechanical compression, and in 77% of those receiving enoxaparin.[6] In comparison, results from this investigation for patients treated with fondaparinux showed that at 5 days postoperatively, 83% of surgical wounds were dry. These results suggest that fondaparinux has comparable wound drainage and subsequent infection risks to either aspirin with mechanical compression or enoxaparin.

Other retrospective studies have shown the benefits of fondaparinux as a prophylactic anticoagulant agent when compared to other anticoagulant agents used after TJA. Agaba et al, reported on the 30-day and 90-day postoperative complications after THA, including pulmonary embolisms (PE) and prosthetic joint infections (PJI), for patients receiving enoxaparin, warfarin, aspirin, or fondaparinux.[16] The authors identified 72,670 THA patients without a history of VTE, 25,966 of which received single medication VTE prophylaxis: 551 (2.12%) aspirin, 6791 (26.15%) enoxaparin, 12,008 (46.25%) warfarin, 5403 (20.81%) rivaroxaban, and 876 (3.37%) fondaparinux[16] and reported that fondaparinux had the lowest risk for DVT at 30 days and 90 days, and a lower risk of postoperative bleeding and thromboembolic events as compared to other VTE prevention agents.[16] These authors

concluded that fondaparinux was associated with a low risk for PE, PJI, and need for transfusion.[16]

Results from this investigation demonstrated a positive correlation between larger BMI and increased length of hospital stay with the use of fondaparinux. These results are consistent with other studies that have reported a similar linear correlation between larger BMI's and increased length of stay as well as increased risk of infection. It has been hypothesized that these results are due to the need for a larger incision and increased fat necrosis from obese TJA patients.[6] Additionally, obese patients are often malnourished[17] which has been shown to interfere with optimal synthesis of collagen and proteoglycans, resulting in disruptions in the wound healing process that can lead to persistent wound drainage and increased risk of infection.[7,18] Patel et al reported that obesity was an independent risk factor for prolonged postoperative wound drainage following total hip arthroplasty regardless of the type of prophylaxis against deep venous thrombosis. This suggests that a BMI greater than 35 may is an independent risk factor for wound drainage irrespective of the anticoagulant used.

This study is the first study to our knowledge to specifically evaluate wound drainage rates, length of hospital stays and infection rates with the use of fondaparinux in total joint arthroplasty patients. Results from this investigation noted that wound drainage and length of stay to be comparable with historic controls with the use of other VTE prophylaxis agents. Patients with BMI greater than 35 kg/m2, appears to be an independent risk factor for wound drainage. The optimal VTE prophylactic regimen is still under debate.[16] Ideally, the best prophylactic agent would provide the most effective defense against VTE events while limiting post-operative complications such as wound drainage, bleeding and infection.[6] Results from this investigation have found that fondaparinux appears to be effective for VTE prophylaxis with wound drainage and infection rates comparable to other anticoagulant agents.

Disclosures

Institutional research funding in direct support of this study was received from GlaxoSmithKline. Each author certifies that his institution approved or waived approval for the use of human subjects for this investigation and that all investigations were conducted in conformity with ethical principles of research.

Conflict of interest

The authors declare that there are no conflict of interest.

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