

FONDAPARİNUSUN KIRIK İYİLEŞMESİNE GERÇEKTEN POZİTİF ETKİSİ VAR MIDIR? SIÇANLAR ÜZERİNDE YAPILAN DENEYSSEL BİR ÇALIŞMA

DOES FONDAPARINUX HAVE REALLY POSITIVE EFFECT ON FRACTURE HEALING?

AN EXPERIMENTAL STUDY IN RATS

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ÖZ

AMAÇ: Antiembolik ajanlar ortopedi ve travmatoloji kliniklerinde özellikle artroplastisi, tümör ve travma cerrahilerinde embolizm problemlerini azaltmak için rutin olarak kullanılmaktadır. Fondaparinux'un kırık iyileşmesi üzerine etkisi belirsizdir. Bu çalışmanın amacı sıçan modeli kullanarak fondaparinuxun kırık iyileşmesi üzerine etkisinin incelenmesi ve enoksaparinin etkisi ile karşılaştırılmasıdır.

GEREÇ VE YÖNTEM: 64 adet Wistar-Albino sekiz gruba randomize olarak ayrıldı. Genel anestezi altında sol femur kapalı standart kırıkları oluşturuldu. Kontrol grupları (A, B), heparin grupları (C, D), enoksaparin grupları (E, F), ve fondaparinux grupları (G, H), sırasıyla izotonik NaCl (1cc/gün), heparin (1000 anti Xa IU/kg/gün), enoksaparin (100 anti Xa IU/kg/gün) ve fondaparinux (0.2mg/kg/gün) olacak şekilde 14 gün süre ile uygulandı. A, C, E, G gruplarındaki sıçanlar postoperatif 14. günün, B, D, F, H gruplarındakiler ise 28. günün sonunda sakrifiye edildiler. Tüm femurların radyolojik incelemesi standart ön-arka ve yan grafiler kullanılarak Goldberg sınıflamasına göre yapıldı. Histolojik inceleme ise Huo histolojik iyileşme sınıflamasına göre yapıldı. Bu çalışmanın istatistiksel analizleri GraphPad Prisma V.3 paket programı kullanılarak yapıldı. Sonuçlarda anlamlılık $p < 0.05$ düzeyi olarak belirlendi.

BULGULAR: Radyolojik incelemede, ikinci ve dördüncü hafta sonundaki sonuçlar incelendiğinde, gruplar arasında istatistiksel olarak anlamlı fark saptanmadı. Histolojik incelemede ise heparin almış olan H grubundaki iyileşme sonuçları diğer gruplarla karşılaştırıldığında istatistiksel olarak anlamlı şekilde kötü olarak saptandı. Diğer gruplar arasında histolojik açıdan, heparin grubu hariç, istatistiksel olarak anlamlı bir fark saptanmadı. Ayrıca histolojik ve radyolojik olarak fondaparinux ve enoksaparin grupları arasında kırık iyileşmesi üzerine etkileri arasında istatistiksel olarak anlamlı fark saptanmadı ($p > 0.05$).

SONUÇ: Çalışmamızda fondaparinuxun enoksaparin ile karşılaştırıldığında kırık iyileşmesi üzerine herhangi ekstra olumlu etkisini saptamadık. Fondaparinux uygulamasının kırık iyileşmesi üzerine negatif bir etkisi saptanmamış olması nedeniyle travma vakalarında embolizm problemlerini önlemede kullanılabileceği kanaatindeyiz.

ANAHTAR KELİMELE: Kırık iyileşmesi, Fondaparinux, Enoksaparin, Heparin, Sıçan

ABSTRACT

OBJECTIVE: Antiembolic agents are routinely used in orthopaedics and traumatology clinics especially in arthroplasty, tumor and trauma surgery to decrease the embolism problems. The effect of fondaparinux on fracture healing is unclear. The aim of this study is to find out the effect of fondaparinux on fracture healing and to compare with the effect of enoxaparin using a rat model.

MATERIALS AND METHODS: 64 Wistar-Albino rats were randomized into eight groups. Standard closed left femur fractures created under general anaesthesia. The control groups (A, B), heparin groups (C, D), enoxaparin groups (E, F), and fondaparinux groups (G, H), which administered isotonic NaCl solution (1cc/day), heparin (1000 anti Xa IU/kg/day), enoxaparin (100 anti Xa IU/kg/day) and fondaparinux (0.2mg/kg/day) respectively for 14 days. The rats in groups A, C, E, G were sacrificed at the end of day 14 and the rats in groups B, D, F, H were sacrificed at the end of day 28 postoperatively. All the femurs were radiologically evaluated with standard AP and lateral X-rays of the sacrificed femurs were rated according to the Goldberg classification system. Histological classification of healing was done according to Huo's histological healing scale. Statistical analysis in this study was performed with GraphPad Prisma V.3 package software. Significance in the results were evaluated at the level of $p < 0.05$.

RESULTS: Radiological evaluation did not reveal any significant difference between the groups in the second and the fourth weeks. Histological callus formation was found to be significantly poorer in the heparin group compared to other groups at the end of the fourth week. No significant differences were found between the groups histologically except the heparin group. Besides that, there was no significant difference on fracture healing radiologically and histologically between the enoxaparin and fondaparinux groups.

CONCLUSION: We did not detect any extra positive effect of fondaparinux on fracture healing compared to enoxaparin. But fondaparinux can be used to prevent embolism problems in traumatic cases as the application of fondaparinux has no negative effect on bone healing.

KEYWORDS: Fracture healing, Fondaparinux, Enoxaparin, Heparin, Rat

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INTRODUCTION

Fondaparinux, warfarin, low-molecular-weight-heparins (LMWH) and unfractionated heparin reduce the risk of deep vein thrombosis (1). One of the major problems in trauma surgery is thromboembolic complications (2). Deep vein thrombosis can occur up to 65% of cases without perioperative anticoagulation (3). Patients with pelvis, lower extremity or vertebral fractures cannot be mobilized preoperatively and some time after the surgery. This perioperative period without mobilization can increase the thrombosis risk up to 60%. As because of this, prophylaxis for thrombosis in trauma patients is indisputable. Mechanic and pharmacologic methods are commonly used together to reduce the risk. But anticoagulant pharmacotherapy is the gold standard thromboprophylaxis for patients undergoing surgery except for the patients who have high risk for bleeding. The efficiency and reliability of pharmacological agents are used for thromboprophylaxis in orthopaedic surgery have been compared and shown LMWHs are superior to heparins and warfarins in preventing DVT and related pulmonary embolism (4, 5).

LMWH effects on bone metabolism and fracture healing are controversial. Most studies have reported adverse effects on bone cycle; however, there are other studies suggesting in the opposite (6-8). Recently, fondaparinux, is one of the popular LMWH reported that it has no negative effects on bone cycle and osteoblasts (9,10) and also fondaparinux is considered to be cost effective and more efficacious than LMWH (1).

As there is limited number of studies about the effects of LMWH on fracture healing; the effect of fondaparinux is not clear (4-12). Up to date, there is not any publication of comparing the effects of heparin, enoxaparin and also fondaparinux in the same study. The aim of this study to compare the effects of heparin, enoxaparin and fondaparinux on fracture healing using a rat femur fracture model. Our hypothesis is fondaparinux would have positive effect on fracture healing compared to enoxaparin.

MATERIALS AND METHOD

Sixty-four male Wistar-Albino rats were used with approval from the Experimental Animals Ethics Committee of the Istanbul University Cerrahpasa Medical School. The study was conducted at the Experimental Animals Research Laboratory of the Istanbul University Cerrahpasa Medical School. The mean age of the rats included in the study was 2.9 months (2.6-3.1 months) and their mean body weight was 195 grams (175-215 grams). The animals were randomly divided into eight groups and 8 animals were placed in each cage named A, B, C, D, E, F, G, and H.

The combination of Ketamine (Ketalar, Pfizer, Istanbul, Turkey) 50mg/kg and Xylazine (Rompun, Bayer, Istanbul, Turkey) was used intraperitoneally for anaesthesia of the rats. The technique which Bonnarens and Einhorn described was used for the animal fracture model (13). Radiographs were taken immediately postoperatively to verify the fracture configuration and the wire placement. Any rats with comminuted fractures excluded from the study. The animals in group A and B were given 1 cc isotonic NaCl solution (I.E Ulugay, Istanbul, Turkey) sc, group C and D were given 100 anti Xa IU/kg of enoxaparin (Clexane, Sanofi-Aventis, Istanbul, Turkey) (14) sc once daily starting from the operation day for two weeks. Also starting from the operation day, 0.2mg/kg fondaparinux (Arixtra, Glaxo Smith Kline's, Istanbul, Turkey) (15-17) sc in group E, F and heparin (Nevparin, Mustafa Nevzat Ilac San, Istanbul, Turkey) 1000 anti Xa IU/kg (18) sc once daily administered for two weeks. The same person did all the injections.

The rats in group A, C, E and G were scarified at the end of day 14 after the operation. The remaining rats were scarified at the end of day 28. Cervical dislocation technique under high dose ether vapour was used for euthanasia. After the rats were killed their left femurs were disarticulated from their hip and knee joints. Soft tissues on femoral bone were peeled off without harming callus tissue. All the left femurs were evaluated for radiological and histological aspects. All the femurs were radiologically evaluated with standard AP and Lateral X-rays of the

sacrificed femurs were rated according to the Goldberg classification system (0= non healing, 1=callus formation but non complete union, 2= complete union) for radiological evaluation (19). Two blind orthopaedic surgeons performed scoring.

For histological evaluation all the femurs were fixed in 10% formalin solution for two weeks time and then fixed in Bouin's solution for another two days. The specimens were embedded in paraffin blocks and cut for 3 micron of 4 sections for each animal. The sections were stained with haematoxylin and eosin. Histological classification of healing was done according to the histological healing scale published by Huo et al. (20) (**Table 1**). All the

Table 1: Scoring system for the histological evaluation

Score	Histologic Findings
1	Fibrous tissue
2	Predominantly fibrous tissue with little cartilage
3	Equal amounts of fibrous tissue and cartilage tissue
4	Only cartilage tissue
5	Predominantly cartilage tissue with little immature (woven) bone
6	Equal amounts of cartilage and immature bone tissue
7	Predominantly immature bone with little cartilage tissue
8	Healing with immature (woven) bone
9	Immature bone with little mature bone
10	Healing with mature (lamellar) bone

histological and radiological results evaluated statistically as the drug treated groups and the control group both in themselves and with each other as well as mutually.

Statistical analysis in this study was performed with GraphPad Prisma Version 3 package software (GraphPad Software, Inc. San Diego, CA, USA). Data evaluation used the Kruskal Wallis test in intergroup comparisons, Dunn's multiple comparison test in subgroup comparisons, the Mann-Whitney U-test in pair group comparisons, and chi-square and Fisher's exact tests in the comparison of qualitative data. Significance in the results were evaluated at the level of $p < 0.05$.

RESULTS

During the postoperative period no complication or death detected. Radiological results according to the mean Goldberg scores and also the results of statistical analyses were

presented in Table 2. Statistically significant correlation was found between the blind orthopaedic surgeons who made the radiologic evaluation. According to Goldberg classification system there was only significant difference in control groups (A (day 14) and B (day 28)) results, the other drug groups showed no significant difference according to their results at day 14 and 28 (**Table 2**).

Table 2: The mean scores and statistical findings of the groups radiologically.

Groups	Day 14	Day 28	p
Control (Name)	(A)	(B)	< 0.05
Mean±Standard Deviation	1,43±0,32	1,87±0,35	
Heparin(Name)	(C)	(D)	> 0.05
Mean± Standard Deviation	1,5±0,46	1,63±0,44	
Enoxaparin(Name)	(E)	(F)	> 0.05
Mean± Standard Deviation	1,63±0,44	1,94±0,18	
Fondaparinux(Name)	(G)	(H)	> 0.05
Mean± Standard Deviation	1,69±0,37	1,75±0,38	
p	> 0.05	< 0.05	

The Goldberg classification system was used for radiological evaluation of fracture healing as (0): non healing, (1): callus formation but non complete union, (2): complete union.

The mean histologic results according to Huo classification were presented in **Table 3**. According to the histologic results there was significant difference between the day 14 and

Table 3: The mean scores and statistical findings of the groups histologically.

Groups	Day 14	Day 28	p
Control (Name)	(A)	(B)	<0.05
Mean±Standard Deviation	3,56±1,24	7±2,56	
Heparin(Name)	(C)	(D)	< 0.05
Mean±Standard Deviation	5,19±2,2	3,37±1,58	
Enoxaparin(Name)	(E)	(F)	< 0.05
Mean±Standard Deviation	3,88±2,57	7,75±2,6	
Fondaparinux(Name)	(G)	(H)	< 0.05
Mean±Standard Deviation	3,81±1,03	6,69±2,69	
p	> 0.05	< 0.05	

The scoring system published by Huo et al (23) was used for histological evaluation. This scale is presented in Table 1.

day 28 scores in each drug groups separately. When the groups were compared according to their results at day 14, there was no significant difference. But there was significant difference among the groups for their day 28 results. The poorest results were in heparin group (group D) which showed significant difference compared to the other drugs and control groups. There was no significant difference among the other groups' (B, F, H) results (**Table 4**).

Table 4: Comparison of each groups' histological results at day 28.

Groups	<i>p</i>
Control Group (B) / Heparin Group (D)	<i>P</i> < 0.05
Control Group (B) / Enoxaparin Group (F)	<i>P</i> > 0.05
Control Group (B) / Fondaparinux Group (H)	<i>P</i> > 0.05
Heparin Group (D) / Enoxaparin Group (F)	<i>P</i> < 0.05
Heparin Group (D) / Fondaparinux Group (H)	<i>P</i> < 0.05
Enoxaparin Group (F) / Fondaparinux Group (H)	<i>P</i> > 0.05

Dunn's Multiple Comparison Test was used to compare each groups results.

DISCUSSION

According to our results fondaparinux has no positive effect on bone healing radiologically and histologically. We also found out that enoxaparin and fondaparinux have no negative effect on fracture healing histologically and radiologically. The negative effect of heparin was detected only histologically when the 4 weeks results were evaluated. Despite the hypothesis of our study; fondaparinux would have positive effect on fracture healing compared to enoxaparin; there was no significant difference between the control, enoxaparin and fondaparinux except heparin that has significantly poorest results.

At the beginning of this study, we thought that heparin and the enoxaparin would affect fracture healing negatively but fondaparinux that has positive effects on osteoblasts according to the previous papers would effect positively on fracture healing (6-12). Hereby, fondaparinux would be used in traumatic patients with fractures safely as an antiembolic agent was a part of our hypothesis. Actually we detected negative effects of heparin on fracture healing but we did not detect the negative effects of enoxaparin on healing. Especially fondaparinux also did not affect the fracture healing in this experimental study.

Thromboembolic complications are still problematic in trauma surgeries both preoperative and especially in the postoperative period. The use of antiembolic agents is absolutely necessary. The major agents that used today are LMWH, fondaparinux and just in case heparin.

Heparin, one of the first used agents used for thromboembolism prophylaxis has negative effects on bone healing and also bone metabolism, which was published in many papers (21-25). Today the use of this agent is limited with the patients who have cardiovascular or neurovascular problems that needs active monitoring. We also found out that heparin has negative effects on fracture healing process especially. The result of this study is consistent with the previous studies in the literature.

LMWH agents are the most popular drugs to prevent thromboembolic events. But according to some publications LMWH have negative effects on fracture healing as heparin (8, 26, 27). There some papers regarding the LMWH have no negative effects on fracture healing (9,27). Also there are some papers concluded that the LMWH can effect bone turnover and healing process negatively when they used for a long time period with high doses (28-30). In our study we found that enoxaparin has no negative effects both radiologically and histologically. This result is similar with previous studies (8, 11, 27). We think that our study follow up is for 4 weeks, which is average for fracture healing process in rats.

Fondaparinux is a synthetic anti-thromboembolic agent that has a selective inhibitor effect on Factor Xa. As it has no effect on thrombin it has no effect on platelet function also (31). There are limited numbers of papers about its activity on fracture healing. Mainly it is believed that fondaparinux has no adverse effect on bone cycle and fracture healing (11). In a study about the effects of dalteparin, enoxaparin, standard heparin and fondaparinux on human osteoblast cells, it was found that fondaparinux has more positive effects according to the

mitochondrial activity and osteoblast protein synthesis. They also concluded that fondaparinux could be used to prevent heparin induced negative effects on fracture healing implant integration (9). According to our study, our results are consistent with that fondaparinux has no negative effect on bone healing. But we could not detect any positive effects on bone healing as they mentioned in their study.

This study also has some limitations. First, lack of biomechanical evaluation. One of the criteria for fracture healing is biomechanical analysis of united fracture. We could not analyse this due to the lack of availability in the laboratory where we conducted our study. The second limitation is the limited kinds of drugs that used in this study. As there were 4 groups in this study the other drugs could be studied such as rivaroxaban, dalteparin, nadroparin. The third limitation is the number of rats and follow up time could be longer for more reliable results.

Up to now, we could not find any study comparing heparin, enoxaparin and fondaparinux in the same experimental fracture model. Radiological evaluations were performed by two orthopaedist independent from the study. It was observed that the evaluation findings of both were in accord with each other.

In conclusion, according to our results showed no significant positive effect of fondaparinux on fracture healing histologically and radiologically comparing the enoxaparin and control groups. We did not detect any extra positive effect of fondaparinux on fracture healing compared to enoxaparin. We think that fondaparinux can be used to prevent embolism problems in traumatic cases as the application of fondaparinux has no negative effect bone healing.

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