

Enoxaparin Use in the Early Postoperative Period after Tibial Nailing is Associated with Significant Increase in Rate of Nonunion and Revision Surgery

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INTRODUCTION: Fracture nonunion is estimated to occur in approximately 2% of all fractures and up to 9% of tibial diaphyseal fractures. Nonunion is associated with patient morbidity including pain, repeat surgeries, and loss of function in addition to significant costs to both the patient and the healthcare system. Efforts have been made to understand and mitigate modifiable risk factors associated with fracture nonunion. Enoxaparin has been identified as a potential risk factor for nonunion following fracture surgery. The purpose of this study was to investigate the relationship between enoxaparin and fracture healing in the early postoperative period in patients undergoing intramedullary tibial nailing for management of diaphyseal tibial fractures.

METHODS:

This is an observational, cross-sectional study. A national insurance database including data from 91 million private insurance, Medicare, and Medicaid patients was queried using Current Procedural Terminology (CPT) codes to identify patients between the ages of 16 and 85 who underwent treatment for tibial shaft fractures between 2015 and 2019. ICD-10 procedural codes were subsequently used to identify only those patients who underwent intramedullary fixation procedures for midshaft tibia fractures. ICD-10 codes and CPT codes were used to identify nonunion and revision surgery.

Logistic regression models were run for nonunion diagnoses and revision surgeries. The following variables were considered: age, sex, CCI, enoxaparin use, tobacco use, obesity, open fracture. Statistical significance and odds ratios (OR) were calculated. We compared the rates of nonunion and revision surgery using covariate models. The covariate model considered enoxaparin in relation to both open fractures and smoking to determine the mathematical of relationship between enoxaparin and other risk factors for nonunion and revision surgery.

RESULTS:

There were 8,677 patients in our cohort who had a tibia shaft fracture treated surgically with an intramedullary nail. Of these, 1,127 (13.0%) received enoxaparin within four weeks of the index surgery. (Table 1)

Tibia fracture nonunion was identified in 337 total patients at a rate of 3.9%. Failure rates were significantly higher for patients with enoxaparin exposure during the four-week postop period compared to those who were not exposed to enoxaparin (6.3% vs. 3.5%, OR = 1.84 (1.41 – 2.41); $p < 0.00001$).

Revision surgery was performed in 223 patients at a rate of 2.6%. Rates of revision surgery were significantly higher for patients with enoxaparin exposure during the four-week postoperative period (5.1% vs. 2.2%, OR = 2.38 (1.72-3.22; $p < .000001$).

A logistic regression analysis of nonunion rates including enoxaparin use, age, gender, obesity, diabetes, tobacco-use, and open fracture demonstrated that enoxaparin use was significantly associated with nonunion with an OR = 1.62 (1.22-2.12). This is similar to risks posed by tobacco use (OR = 1.50) and obesity (OR = 1.79). (Table 2)

Similarly, logistic regression analysis of revision surgery rates demonstrated that enoxaparin use was significantly associated with revision surgery with an OR = 2.05 (1.49 -2.80). This a higher risk profile compared to tobacco use (OR=1.61) and was similar to the risk posed by obesity (OR = 1.90). Only open fracture had significantly higher association with revision surgery (OR = 3.65). (Table 3)

DISCUSSION AND CONCLUSION: In our analysis of the sample of 8,677 patients who received intramedullary fixation for tibia fractures, a significantly higher proportion of patients exposed to early enoxaparin experienced nonunion and revision surgery compared to patients not exposed to enoxaparin. We found that the risk profiles for enoxaparin use with nonunion (OR=1.6) and revision surgery (OR=2.0) were comparable to those of tobacco use and obesity. The clinical effects of LMWH on bone development and maintenance have not been studied extensively, though there is limited in vitro and animal model evidence suggesting deleterious effects of LMWH on bone healing. This is the first human study to show a definitive effect of enoxaparin on fracture healing and suggests the need for careful consideration of VTE prophylaxis use in patients with fractures.

	Enoxaparin (n = 1127)	No Enoxaparin (n = 7550)	Significance
Age			
Mean (SD)	45.4 (17.2)	50.9 (18.6)	p < 0.0001
CCI			
Mean (SD)	1.47 (2.38)	2.15 (2.88)	p < 0.0001
Gender			p = 0.42
Female	514 (46%)	3545 (47%)	
Male	613 (54%)	4005 (53%)	
Obesity			p = 0.84
Yes	327 (29%)	2217 (29%)	
No	800 (71%)	5333 (71%)	
Diabetes			p < 0.0001
Yes	239 (21%)	2300 (30%)	
No	888 (79%)	5250 (70%)	
Tobacco Use			p = 0.62
Yes	318 (28%)	2188 (29%)	
No	809 (72%)	5362 (71%)	
Open fracture			p < 0.0001
Yes	401 (36%)	2135 (28%)	
No	726 (64%)	5415 (72%)	

Parameter	Estimate	Std. Error	z Value	P-Value
Age	-0.00116	0.003558	-0.325	0.7455
Male Gender	0.46683	0.124093	3.762	0.0002
CCI	-0.05417	0.030215	-1.793	0.073
Obesity	0.586523	0.12424	4.721	<0.0001
Tobacco Use	0.402198	0.118995	3.38	0.0007
Diabetes	-0.26416	0.158726	-1.664	0.0961
Enoxaparin Open	0.48287	0.14049	3.437	0.0006
Fracture	1.067465	0.116815	9.138	<0.0001

Parameter	Estimate	Std. Error	z Value	P-Value
Age	-0.00558	0.004413	-1.265	0.206
Male Gender	0.337277	0.150234	2.245	0.0248
CCI	-0.0527	0.037331	-1.412	0.158
Obesity	0.640681	0.150447	4.259	<0.0001
Tobacco Use	0.473837	0.14374	3.296	0.001
Diabetes	-0.11681	0.192218	-0.608	0.5434
Enoxaparin Open	0.719917	0.160426	4.488	<0.0001
Fracture	1.29493	0.145483	8.901	<0.0001