Impact of Smoking on Fracture Healing and Risk of Complications in Limb-Threatening Open Tibia Fractures

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Objectives: Current data show smoking is associated with a number of complications of the fracture healing process. A concern, however, is the potential confounding effect of covariates associated with smoking. The present study is the first to prospectively examine time to union, as well as major complications of the fracture healing process, while adjusting for potential confounders.

Setting: Eight Level I trauma centers.

Patients: Patients with unilateral open tibia fractures were divided into 3 baseline smoking categories: never smoked (n = 81), previous smoker (n = 82), and current smoker (n = 105).

Outcome Measure: Time to fracture healing, diagnosis of infection, and osteomyelitis.

Methods: Survival and logistic analyses were used to study differences in time to fracture healing and the likelihood of developing complications, respectively. Multivariate models were used to adjust for injury severity, treatment variations, and patient characteristics

Results: After adjusting for covariates, current and previous smokers were 37% ($P = 0.01$) and 32% ($P = 0.04$) less likely to achieve union than nonsmokers, respectively. Current smokers were more than twice as likely to develop an infection ($P = 0.05$) and 3.7 times as likely to develop osteomyelitis ($P = 0.01$). Previous smokers were 2.8 times as likely to develop osteomyelitis ($P = 0.07$), but were at no greater risk for other types of infection.

Conclusion: Smoking places the patient at risk for increased time to union and complications. Previous smoking history also appears to increase the risk of osteomyelitis and increased time to union. The results highlight the need for orthopaedic surgeons to encourage their patients to enter a smoking cessation programs.

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Cigarette smoking has been shown to be a risk factor for a variety of diseases and conditions, including cancer and coronary heart disease.[1,2] Orthopedic surgeons have long suspected a link between smoking and complications of the fracture healing process. Several studies have provided preliminary evidence of a link between smoking and delayed healing,[3–16] nonunion,[2,3,7,9,13,17–23] infection,[21,24–28] and osteomyelitis,[26,29] whereas some studies have failed to observe these effects.[3,30] Laboratory studies have shown that nicotine reduces vascularization at bone healing sites,[31] and this is associated with delayed healing in animal models.[28,31] Smoking also appears to decrease immune functions.[32]

A concern with the current studies, however, are the potential confounding effects of injury severity and covariates associated with smoking, such as age, overall health status (including health habits and nutritional status), education, and socioeconomic level.[33,34] Socioeconomic status has been shown to affect overall health status,[29,35] as well as factors like availability of insurance and access to treatment,[17,36] treatment compliance and health behaviors,[24,37] and psychosocial health.[25,38] The few studies that have examined the relationship between smoking and outcome have not adequately controlled for potential differences at baseline. The present study examines the effect of smoking on time to union and major complications of the fracture healing process, within the context of a prospective study with sufficient power to allow adjustment for variations in treatment, patients, and injury characteristics. We hypothesized that smokers experience a longer time to fracture healing and have higher rates of major infections and osteomyelitis. The study hypothesis was tested using a subgroup of patients who were participants in the Lower Extremity Assessment Project (LEAP). The Lower Extremity Assessment Project is a cohort study of lower extremity trauma patients who were at risk for amputation.[39] The primary goal of the LEAP study was to examine the outcomes related to the decision to reconstruct or amputate the injured leg. In previ-

ously published LEAP data focusing on the entire cohort, smokers are shown to have worse Sickness Impact Profile (SIP) scores at 2 years than nonsmokers.[8] The present analysis focuses on the subset of this population comprising 268 open tibia fracture patients entered into the salvage pathway.

METHODS

Study Population

Eligible patients were between the ages of 16 and 69 years and admitted for treatment of lower extremity trauma below the distal femur. Inclusion and exclusion criteria for entry into the study have been reported earlier[18] and are summarized in Table 1. These criteria were established to identify patients at risk for amputation who did not have significant injuries to the central nervous system or a pre-existing mental health problem that would compromise recovery. The 8 participating centers were level I trauma centers. Study protocol stipulated the involvement of an orthopaedic attending during the initial evaluation and treatment of all major limb trauma cases. All patients were treated with a protocol that included aggressive fracture debridement, antibiotic coverage, fracture stabilization, repeat debridement, and early soft tissue coverage. Fractures with bone loss or that showed no progression to union underwent fracture stimulation procedures, including bone grafting, rod dynamization, repeat reamed nailing (exchange nail), fibular osteotomy, and ultrasound/electrical stimulation, which were selected and timed at the discretion of the treating surgeon. The present analysis examines 268 patients with unilateral open tibia fracture entered into the reconstructive treatment pathway of the LEAP study. Demographics for participants in this study have been reported elsewhere.[18,39] Briefly, this subset was composed of 73% males, had a mean age of 33.4 years, was 80% white, and had 27% without a high school diploma and 42% with household incomes under the federal poverty line. For this analysis, the study group was divided into 3 smoking categories: never smoked (n = 81), previous smoker (n = 82), and current smoker (n = 105). Smoking status was based on the responses to 2 questions: a) whether the patient had smoked 100 or more cigarettes over the course of his or her lifetime; and b) whether the patient was currently smoking. Patients who were either currently smoking or had a smoking history were advised about the negative impact of smoking on their health.

TABLE 1. LEAP Study: Inclusion and Exclusion Criteria

A.	Inclusion Criteria
1.	Traumatic amputations below distal femur
2.	Gustilo Grade IIIA tibia fracture with length of hospital stay >4 days and 2 or more surgical limb procedures and 2 or more of following: a) severe muscle damage (>50% loss of 1 or more major muscle groups or associated compartment syndrome with myonecrosis; b) associated nerve injury (posterior tibial or peroneal deficit); c) major bone loss or bone injury (associated fibula fracture and >50% displacement, comminution and segmental type fracture, and >75% probability of requiring bone graft/transport)
3.	Gustilo Grade IIIB tibia fracture
4.	Gustilo Grade IIIC tibia fracture
5.	Dysvascular injuries below distal femur excluding foot including: knee dislocations, closed tibia fractures, and penetrating wounds with vascular injury documented from arteriogram, surgery, or ultrasound
6.	Major soft tissue (ST) injuries below distal femur excluding foot including: AO type IC3 IC5 degloving injuries, severe ST crush/avulsion injuries with muscle disruption or compartment syndrome, compartment syndrome resulting in myonecrosis and requiring partial or full muscle unit resection, severe foot injuries including: Gustilo Grade III B open ankle fractures, severe open hind or midfoot injury (ie, either insensate plantar surfaces, devascularization, major degloving injury or open soft tissue injury requiring coverage), open grade III pilon fractures
B.	**Exclusion Criteria**
1.	Patient is younger than 16 or older than 69
2.	Transfer <24 hrs from time of injury or primary orthopaedic treatment elsewhere
3.	Glasgow Coma Scale (GCS) score <15 at 21 days or discharge, if sooner
4.	Spinal cord deficit
5.	Prior leg or foot amputation or nonambulatory preinjury
6.	3rd degree burn on injured leg that measures more than 1 handbreadth
7.	Documented psychiatric disorder or mental retardation
8.	Non-English or non-Spanish speaking
9.	On active military duty
10.	Lived outside catchment area of trauma center

Procedures

Patients were enrolled in the study over a 40-month period (March 1994–June 1997) and followed prospectively at 3, 6, 12, and 24 postinjury. Prior to hospital discharge, patients were assessed by a physical therapist and interviewed by the study coordinator. At each follow-up, they were asked to participate in: 1) an orthopedic evaluation to ascertain the occurrence of complications and status of the limb; 2) an evaluation by a physical therapist to ascertain extent of impairment; and 3) an interview to measure the patient's perception of his or her functional status and overall sense of well-being. Patient medical records were abstracted following initial hospital discharge and following each rehospitalization over the follow-up period.

Characterizing Patients and Their Injuries

Extensive data were collected on patient environment, demographics, and health habits, including: income level,

years of education, age, previous chronic conditions, race, gender, alcohol and drug consumption, health insurance, personality type, health status at baseline (including ability to climb stairs, run, walk, and exercise), previous leg injuries, availability of social support, and self-efficacy for return to work. All leg injuries were prospectively classified at the time of admission and underwent soft tissue coverage using standard classifications and limb salvage indices proposed in the literature. For the analysis, injuries were summarized according to: i) type and extent of bony injury using the OTA classification of tibia fractures,[13] AO classification of tibia fractures,[40] the Hannover fracture scale,[16] the limb salvage index,[41] and the predictive salvage index[42]; ii) the extent of skin, neurovascular, muscle, and tendon injury using the AO classification of soft tissue injury of tibia, the Hannover fracture scale, the limb salvage index, and the predictive salvage index; iii) plantar sensation and shock as defined by the Mangled Extremity Severity Score[43]; and iv) overall tibia fracture assessment using the Gustilo classification.[44] Associated injures were classified using the Abbreviated Injury Scale (AIS)[4] and the Injury Severity Scale (ISS) score[6]; 2 scores denoting the maximum AIS severity of contralateral and ipsilateral nonamputation threatening leg injuries were also computed.

Outcome Measures

The primary outcome measures used in the present analysis were time to fracture healing and the diagnosis of wound infection or osteomyelitis requiring inpatient treatment (rehospitalization). A surgeon assessed fracture-healing status by recording the number of weeks between admission and union. Fracture healing was defined using both radiographic union (bridging of the fracture site) and clinical assessment, specifically when the patient is able to bear weight and perform activities and experiences no pain at the fracture site. For a significant number of patients, union was achieved after surgical intervention (as described in the *Study Population* section above).

Wound infection was defined as soft-tissue infection not involving the bone and treated with local debridement and short-term antibiotics. In this analysis, we report only the cases of wound infection resulting in inpatient treatment (rehospitalization), because a very large proportion of the study group (>80%) was diagnosed as having a wound infection and treated on an outpatient basis during the first 6 months of follow-up. Although complications treated on an outpatient basis were not observed to have a significant effect on outcome, rehospitalization due to a complication was a strong predictor of poor function at 2 years.[18] Osteomyelitis was defined as an infection involving the bone and treated with bone debridement and long-term antibiotics. All cases of osteomyelitis in this study were treated on an inpatient basis. In addition to the complications reported here, a number of other complications were observed. These complications were less common than wound infection and osteomyelitis.

Data Analysis

All outcome measures were examined using multivariate regression techniques to adjust for the effects of potential confounders. Exploratory techniques were used to examine the relationship between outcome measures and each of the hypothesized covariates (χ^2 tests, t tests, and analysis of variance [ANOVA] tests), the extent of correlation among the covariates (Pearson correlation coefficients), and the within-patient correlation in the response data.[23] No 2 covariates were sufficiently colinear to be redundant, and the modest within-patient correlation did not necessitate complex modeling of autocorrelation. Time to fracture healing was studied using standard survival analysis. Estimation of regression effects was accomplished using the Cox proportional hazards regression model. Estimates of the variance of effects estimators were employed in constructing confidence intervals. Individuals who did not heal by 2 years were included in the analysis as censored observations, thus contributing to the analysis up until the time of the last available follow-up. Development of complications was studied using both logistic and Poisson regression analyses. Substantive conclusions remained the same under either method; the logistic regression results are reported. All of the variables mentioned above were evaluated in the models, including investigation of possible interaction terms.

RESULTS

Follow-up Rates

Current and past smokers were significantly more likely to be lost to follow-up over the 2 years of the study. At 24 months, 91.4% of patients in the "never smoked" category were interviewed, as opposed to only 85.4% and 76.2% in the "previous smoker" and "smoker" categories ($P < 0.01$, in both cases). Patients lost to follow-up were also more likely to be nonwhite and less educated than followed patients (data not shown).

Clinical Outcomes

Table 2 summarizes the time to fracture healing and the percent with infection and osteomyelitis as a function of smoking status and other variables observed to be important predictors of outcome. Nonsmokers appear more likely to heal by 24 months, but because time-to-outcome measures are only available for patients who achieved that outcome, differences between groups can be misleading. Survival analysis becomes necessary to obtain estimates of differences in time to healing between groups. Nonsmokers also appear less likely to develop infections and osteomyelitis. Over the course of the follow-up, these complications resulted in 1.2 ± 1.4 surgeries in the nonsmoking group, 1.4 ± 1.4 surgeries in the previous

TABLE 2. Time to Healing and Incidence of Infection and Osteomyelitis by Selected Covariates at Two Years of Follow-Up

	N	% Unhealed Fracture at 24 Months	Time to Fracture Healing (in Wks)*	% With Infections	% With Osteomyelitis
Smoking status at baseline					
Never smoked	81	9.9	40.1	14.8	4.9
Quit smoking	82	11.0	47.8	13.4	13.4
Current smoker	105	24.1	42.9	24.8	17.1
Bone loss/damage					
Mild damage	55	10.2	41.9	9.1	7.3
Moderate damage	155	14.9	42.8	16.1	10.3
Bone loss <2 cm	25	11.1	41.8	24.0	16.0
Bone loss >2 cm	33	30.8	54.7	39.4	27.3
Muscle damage					
AO MT 1 2	131	11.4	40.7	14.6	12.2
AO MT 3 4	117	6.7	45.6	23.1	13.7
AO MT 5	20	21.4	54.1	25.0	5.0
Fracture stimulating surgery					
None	112	7.1	37.2	9.8	6.3
1 or more	156	20.3	48.1	24.4	16.7
Tibia fracture classification					
IIIA	55	6.0	42.7	9.1	5.5
IIIB	74	18.5	46.5	14.9	10.8
IIIC	139	17.2	39.4	23.7	15.8
Social support					
Low	65	24.5	49.1	18.5	16.9
Medium-high	203	12.9	42.5	18.0	11.0
Education					
Less than high school	77	21.9	40.5	24.7	15.6
High school	104	16.0	44.2	18.3	10.6
Some college	87	10.2	45.3	12.6	11.5
Injury severity score					
<13	168	13.3	44.9	18.5	9.5
>13	100	18.3	41.4	18.0	17.5
Total	268	15.4	43.6	18.3	12.5

*Among those healed.
MT, Muscle/tendon injury.

smoker group, and 1.5 ± 1.7 surgeries in the smoking group ($P < 0.05$, ANOVA).

Multivariate Regression Models

We developed multivariate regression models to adjust for the effect of differences in patient, treatment, and injury characteristics. Time to fracture healing was analyzed using a survival model and results reported as hazard ratios. Often, survival models use death as the outcome, and the hazard ratio is interpreted as the increase in risk associated with being a smoker versus a nonsmoker across all time points. In this analysis, the outcome (healing) is a positive one, and hence, increased hazard is in fact desirable. The results of this adjustment are presented in Table 3. After adjusting for covariates, we estimate that over the course of the follow-up (2 years) current smokers were 37% less likely to be healed than nonsmokers ($P = 0.01$), whereas previous smokers were at 32% less likely to be healed than nonsmokers ($P = 0.04$).

Separate logistic regression models were developed for the 2 major complications: infection and osteomyelitis. In these models, the outcome (development of a complication) is a negative one, and the odds ratio (OR) is interpreted in the usual manner. The results of the infection and osteomyelitis analyses are presented in Table 4. After adjusting for covari-

TABLE 3. Survival Analysis: Time to Tibia Fracture Healing After Adjustment for Patient, Treatment, and Injury Characteristics*

	Hazard Ratio (95% Confidence Interval) *P*
Never smoked†	1.00
Quit smoking	0.680 (0.97 0.47) $P = 0.03$
Current smoker	0.630 (0.90 0.44) $P = 0.01$

*Adjusted for bone loss greater than 2 cm, ISS greater than 13, moderate to severe muscle injury (as defined by AO classification Muscle/Tendon injury greater than 2), low social support, Gustilo classification tibia fracture greater than IIIA, having less than a high school education, and having required fracture stimulating surgery.

†Reference category.

ates, current smokers were more than twice as likely (OR = 2.2) to develop an infection than nonsmokers ($P = 0.05$), whereas previous smokers were at no greater risk (OR = 1.0) than nonsmokers. After adjusting for covariates, current smokers were 3.7 times as likely to develop an osteomyelitis than nonsmokers ($P = 0.01$), whereas previous smokers were 2.8 times as likely to develop osteomyelitis than nonsmokers, although this difference was not statistically significant at the $P < 0.05$ level ($P = 0.07$).

In all models, additional factors associated with increased time to healing and increased likelihood of infection and/or osteomyelitis were: bone loss greater than 2 cm, ISS greater than 13, moderate to severe muscle injury (as defined by AO classification Muscle/Tendon injury greater than 2), low social support, Gustilo IIIB or IIIC tibia fracture, having less than a high school education, and having required fracture stimulating surgery (data not shown).

TABLE 4. Logistic Regression Analyses: Likelihood of Developing Infection or Osteomyelitis After Adjustment for Patient, Treatment, and Injury Characteristics*

	Odds Ratio (95% Confidence Interval) *P*	
	Infection	**Osteomyelitis**
Never smoked†	1.00	1.00
Quit smoking	1.00 (2.48 0.40) $P = 0.99$	2.80 (8.83 0.89) $P = 0.07$
Current smoker	2.22 (4.91 1.01) $P = 0.05$	3.72 (11.1 1.25) $P = 0.01$

*Adjusted for bone loss greater than 2 cm, ISS greater than 13, moderate to severe muscle injury (as defined by AO classification Muscle/Tendon injury greater than 2), low social support, Gustilo classification tibia fracture greater than IIIA, having less than a high school education, and having required fracture stimulating surgery.

†Reference category.

DISCUSSION

Smoking at the time of injury places the tibia fracture patient at significant risk of increased time to union, as well as increased likelihood of developing complications. Previous smoking history also appears to place the patient at increased risk of poor outcomes. The results observed in the "previous smoker" group may reflect the lingering effects of past smoking. Alternatively, "previous smokers" have been shown to suffer from relapse rates of greater than 50%,[45] and the results may reflect the effects of a significant percentage of this group reverting to smoking during the follow-up period. Because the assessment of smoking status was based on self-report, it is also possible that some patients in the "previous smoker" group were in fact current smokers, a phenomenon observed in other settings.[5,45,46] In this sense, the "previous smoker" group might be interpreted as a combination of current and previous smokers rather than a homogeneous group. This would also be the case in the likely scenario of a fraction of "previous smokers" relapsing during the follow-up.

A number of important limitations of this study must be noted. First, smoking status was only assessed at baseline. However, if patients changed their smoking status during follow up, this would likely result in smaller observed differences between groups. Thus, it is likely that the actual effects may in fact be greater than the data indicate. A second limitation is that follow-up rates were different among comparison groups, with smokers and previous smokers having higher rates of loss to follow-up. Because patients lost to follow-up appear to have worse outcomes than patients followed, it seems reasonable to assume that the differences between groups would be even greater if all patients had been followed. A third limitation in this analysis is the possibility of confounding, as it is possible that smoking status is related to a number of characteristics associated with poor outcomes, such as socioeconomic status, health habits, treatment compliance, and employment characteristics, among many others. Although in this analysis the results of the multivariate analysis essentially confirmed the results of the bivariate analysis, it is still possible for residual confounding to persist, or that additional patient characteristics have not been accounted for in our study. Fourth, as has been noted above, the assessment of smoking status suffers from the limitations of self-reported data. Fifth, time to fracture healing was assessed by different surgeons at different sites, and it is possible that interobserver variability might have altered the results of this study. Finally, it must be noted that both because of lack of more specific data and sample size limitations, participants were classified into 3 broad smoking categories (smoker, never smoked, quit smoking). The use of such categories does not allow for important distinctions be-

tween, for example, those who quit months versus decades before the beginning of the study, or those who smoked less than 1 versus multiple cigarette packs per day.

It is important to emphasize that although previous smokers were at increased risk of delayed union and complications, their risk was not as great as that of current smokers. Given the risk of delay in fracture healing, these patients might be candidates for osteoinductive therapies at the time of first revision surgery and/or active ultrasound devices,[47] though further research needs to be done to show these interventions to be effective. These results highlight the need for orthopaedic surgeons to encourage their patients to enter a smoking cessation programs at the time of initial hospital discharge.

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