Acta Orthop. Belg., 2012, **78**, 285-290

REVIEW ARTICLE

The effect of smoking on fracture healing and on various orthopaedic procedures

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Ten percent of all fractures lead to problems with healing. Smoking is said to be a cause. There are 13.5 million smokers in the UK. Healing of tibial fractures, for instance, requires two more months in smokers. Nicotine, carbon monoxide and hydrogen cyanide are most often seen as the offenders, among the 4000 chemicals found in cigarettes. Many studies plead for the negative effect of smoking in general, yet there is uncertainty as to the precise role of nicotine. The authors recommend that patients should attempt smoking cessation therapy before elective orthopaedic treatment.

Keywords : smoking ; nicotine ; carbon monoxide ; fracture ; non-union.

INTRODUCTION

Fracture healing is a complex process where biological, mechanical and systemic factors affect the rate of healing and ultimately the possibility of non-union and infection. Of the estimated 1.3 million fractures per year in the United Kingdom, an estimated 10% have a problem with healing (*25*). Causes of non-union may be related either to the fracture (type and site of fracture, degree of comminution, infection, instability, vascular injury) or to systemic factors including diabetes (*4*), peripheral vascular disease (*14*), and non-steroidal anti-inflammatory drugs (NSAIDS) (*6*). Smoking has a well documented negative effect on the cardiac and respiratory systems. The current study tries to bring in arguments for a similar negative effect on bone healing.

There are 4000 chemicals found in cigarettes (*29*). Nicotine, carbon monoxide and hydrogen cyanide are often cited as the causes of adverse effects. However the exact mechanism and effect of smoking on fracture healing has yet to be established. With an estimated 13.5 million smokers in the UK (representing 22% of the population (*33*)) the possible impact of smoking on fracture healing is clearly important and clinically relevant.

Giannoudis *et al* (*18*) described a "diamond concept of requirements" for fracture healing to occur successfully : osteogenic cells, osteoconductive scaffold, mechanical stability and adequate growth factors. Whilst it is unlikely that smoking affects the mechanical stability, it may have effects on the other three aspects of the diamond.

This review discusses the clinical effects of smoking on fracture healing and its possible mechanisms, including possible causative chemicals.

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No benefits or funds were received in support of this study

Furthermore it focuses on the effect of smoking on specific fracture sites. Fracture healing is a complex phenomenon, the details of which will not be discussed here.

TOXIC EFFECTS OF SMOKING

Smoking in general

Smoking releases norepinephrine from adrenergic axon terminals within the tissues in the plasma of volunteers (*11*). Subcutaneous wound-tissue oxygen falls rapidly and significantly in response to smoking, and remains low for 30 to 50 minutes (*24*). In human umbilical vein endothelial cells, cigarette smoke extracts inhibit VEGF (Vascular Endothelial Growth Factor) -induced tube formation in the matrigel assay ; these findings might contribute to explain the negative effect of cigarette smoking on endothelial function and vessel growth (*31*).

Dintenfass (*15*) studied blood viscosity factors in 125 male smokers and non-smokers. The smokers exhibited significantly elevated haematocrit values, fibrinogen levels and blood viscosity ($p < 0.025$)), and increased aggregation of red cells and plasma viscosity ($p < 0.005$).

Thus smoking seems to have negative effects, but is it the nicotine which is at the origin ?

Nicotine

Nicotine is the principal alkaloid of tobacco, and is its main addictive component. Theiss *et al* (*37*) administered it to 24 New Zealand White rabbits after posterolateral lumbar fusion. It inhibited expression of a wide range of cytokines in the central fusion mass : the cytokines associated with neovascularization and osteoblast differentiation. Therefore, the effects of nicotine appear to involve more than just local vasoconstriction.

Raikin *et al* (*34*) performed midshaft tibial osteotomies in 40 New Zealand White rabbits. They were randomized to nicotine or saline. Three (13%) osteotomies showed no clinical evidence of union in the nicotine group, whereas all fractures in the control group healed. Biomechanical testing showed the nicotine exposed bones to be 26% weaker in three-point bending. These findings were reinforced by Hollinger *et al* (*21*) who found that nicotine adversely affected autograft incorporation and depressed donor site healing in parietal bone defects prepared in 60 Long-Evans rats.

Daftari *et al* (*12*) transplanted autologous cancellous bone to the anterior chamber of the eye in 24 rabbits. Half of the rabbits received nicotine and half received placebo (albumin) from mini-osmotic pumps which were implanted subcutaneously. Nicotine, as compared with placebo, was associated with delayed revascularization within the graft and a smaller percent area of revascularization, while a larger number of grafts showed necrosis.

Others found no correlation between impaired bone healing and nicotine. Gullihorn *et al* (*20*) exposed *in vitro* cultures of MC3T3-E1 osteoblast-like cells to varying doses of nicotine or condensates of cigarette smoke. Metabolic assays included alkaline phosphatase activity, collagen synthesis, and total protein synthesis as well as cell proliferation. Nicotine elicited a significant dose-dependent stimulation of bone cell metabolism ! On the other hand, preparations of smoke condensate with equivalent nicotine concentrations reduced all indices of metabolic activity. A probable speculation is that the delay in clinical healing of skeletal trauma in smoking patients may in part be a result of absorption of components of smoke other than nicotine.

Carbon monoxide

Smoking increases the concentration of carbon monoxide (CO) in the blood. It binds to haemoglobin with a higher affinity than oxygen to form carboxyhaemoglobin, thereby reducing the oxygen carrying capacity, causing tissue hypoxia. The treatment for carbon monoxide poisoning is high flow oxygen or hyperbaric oxygen (HBO).

Ueng *et al* (*38*) lengthened the right tibia in 18 rabbits, which were randomised to either smoking with HBO, non-smoking or smoking. Bone mineral density of the right tibia and torsional strength of the contralateral tibia were measured. The smoking group had the worst outcome. They concluded that smoke inhalation delays the bone healing in tibial

Table I. — Review of the literature : effect of smoking on upper limb surgery

1st author	year	region	number of patients	treatment	test	results
Chen	2001	ulna	20 smokers 20 non-smokers	shortening osteotomy	union	- 7.1 months in smokers - 4.1 months in non-smokers - 30% nonunion in smokers - 0% nonunion in non-smokers
Little	2006	scaphoid-fracture	64 patients	bone graft & screw fixation	union	- 13 of 17 nonunions were smokers
van Adrichem	1992	digit	31 patients	replantation	vascularity	- acute smoking decreased vascularity in 14 smokers, but increased it in 17 non-smokers

lengthening ; however, HBO mitigates the delayed healing effect of smoke inhalation and, thus, helps the smoking animal in achieving an expeditious bone healing in tibial lengthening.

It is not clear whether nicotine, carbon monoxide or both are responsible for the negative effect of smoking on fracture healing.

EFFECT OF SMOKING ON VARIOUS ORTHOPAEDIC PROCEDURES

Upper Limb

Chen *et al* (*10*) (Table I) retrospectively evaluated 40 ulnar shortening osteotomies. The average healing time was 7.1 months in smokers, compared to 4.1 months in non-smokers. Little *et al* (*28*) found that of 64 patients with scaphoid fractures, treated with bone grafting and screw fixation, 17 went on to nonunion ; 13 of these were smokers ($p = 0.005$).

van Adrichem *et al* (*39*) studied the microcirculation of the skin in 31 patients who had undergone digital replantation or revascularization. Fourteen smokers showed a mean decrease in laser Doppler flow of 8% and 19%, during smoking of a first and a second cigarette respectively, whereas 17 non-smokers showed a slight increase of 4% and 4%, respectively.

Spine

The effect of smoking on spinal degeneration appears to be multifactorial : smoking is a risk factor for low back pain, disc herniation and osteoarthritis (*1,17*) (Table II). It has been shown to be a risk factor for degenerative changes in the absence of genetic variation as shown by magnetic resonance imaging in identical twins (*2,3*). It has been suggested that nicotine inhibits the revascularization of cancellous bone grafts used in spinal fusion.

Brown *et al* (*5*) studied 100 patients who underwent a 2-level laminectomy and fusion ; the non-union rate was 40% in the smoking group and 8% in the non-smoking group ($p = 0.001$). Glassman *et al* (*19*) found further causal evidence when they assessed the rate of spinal fusion in patients who stopped smoking after spinal fusion. The rate of nonunion in smokers was almost double that of non-smokers (26.5% versus 14.2%) ($p < 0.05$). However, the rate was also significantly reduced in those who stopped smoking for more than 6 months postoperatively : 17.1%. More than 90% of those who stopped smoking had no nicotine replacement therapy.

Lower limb

Castillo *et al* (*7*) (Table III) studied 268 limb-threatening open tibia fractures. Current smokers were 37% ($p = 0.01$) less likely to achieve union, and previous smokers 32% ($p = 0.04$) less likely than non-smokers.

Kyrö *et al* (*27*) studied a total of 135 patients with a fresh tibial shaft fracture who underwent primary conservative treatment. The smokers were found to have a significantly longer mean time to clinical union (23.7 weeks versus 19.1 weeks) and a higher incidence of non-union : 50% versus 32%.

Table II. — Review of the literature : effect of smoking on spinal fusion

1st author	year	region	number of patients	treatment	test	results
Brown	1986	spine	50 smokers 50 non-smokers	2 level laminectomy and spinal fusion	union	- 40% nonunion in smokers - 8% nonunion in non-smokers
Glassman	2000	spine	357	fusion	union	- 26.5% nonunion in smokers - 17.1% nonunion in ex-smokers - 14.2% nonunion in non-smokers

Table III. — Review of the literature : effect of smoking on healing of lower limb fractures

1st author	year	region	number of patients	treatment	test	results
Castillo	2005	open tibia #	105 smokers 82 ex-smokers 81 non-smokers	IM nail & bone stimulant	union	- smokers 37% less chance of healing - previous smokers 32% less chance of healing
Moghaddam	2011	tibia	39 non-smokers 45 smokers	IM nail/ external fixator	time to union	- 17.4 weeks for smokers - 11.9 weeks for non-smokers
Kyrö	1993	tibia	135	conservative	time to union revisions	- 23.7 weeks for smokers - 19.1 weeks for non-smokers - 50% in smokers - 32% in non-smokers
Schmitz	1999	open tibia # GA I	44 smokers 59 non-smokers	IM nail / external fixator / cast	time to union non-unions	- 38.4 weeks for smokers - 19.4 weeks for non-smokers - 2 smokers - 0 non-smokers
Hoogendoorn	2002	open tibial #	46 smokers 72 non-smokers		time to union	- 33 weeks for smokers - 26 weeks for non-smokers
W-Dahl	2004	tibia hemi-callotasis	166 non-smokers 34 smokers	external fixation	delayed union	- 41% delayed union in smokers - 15% delayed union in non-smokers
McKee	2003	limbs Ilizarov reconstruction	39 non-smokers 47 smokers 86 Ilizarovs in 84 pts	Ilizarov	union infection amputation	- 10 vs 2 nonunions - 7 vs 1 infections - 5 vs 0 amputations

McKee *et al* (*30*) retrospectively reviewed 84 patients who underwent 86 Ilizarov reconstructions. There was a higher incidence of nonunion in the smoking group : 10 versus 2 ($p = 0.031$). Seven of eight patients with persisting infection were smokers ($p = 0.049$). All five amputations were in smokers ($p = 0.035$). There were significantly more poor results in the smoking group than in the non-smoking group (18/47, 38% versus 4/39, 10% ; $p = 0.003$).

Four studies (*22,27,32,35*) compared the healing time of tibial fractures in smokers and non-smokers : the difference was about 2 months.

Foot and ankle

Subtalar and tibiotalocalcaneal athrodeses may be performed for symptomatic osteoarthritis not relieved by conservative procedures. They have shown to provide excellent symptomatic response once union had occurred. Common complications include delayed/non-union, wound infection and leg length discrepancy (*9*).

Cobb *et al* (*10*) conducted a case controlled study on 44 patients undergoing ankle arthrodesis and found a 3.75 times greater risk of nonunion in the 22 smokers. The results only approached statistical

Table IV. — Review of the literature : effect of smoking on foot and ankle surgery

1st author	year	region	number of patients	treatment	test	results
Cobb	1994	ankle	22 smokers 22 non-smokers	arthrodesis	union	- 3.75 × greater risk of nonunion in smokers
Ishikawa	2002	ankle	80 smokers 80 non-smokers	hindfoot fusion	union	- 2.7 × greater risk of nonunion in smokers
Krannitz	2009	foot	17 smokers 12 ex-smokers 17 non-smokers	Austin bunionectomy	union	-17.1 weeks for smokers -11.1weeks in ex-smokers - 9.9 weeks in non-smokers

significance, due to small patient numbers. Ishikawa *et al* (*23*) also found an increased chance of nonunion after hindfoot fusions in smokers (2.7 times), while patients who had stopped smoking for more than 6 weeks had a significantly lower chance of nonunion, however still higher than non-smokers. To further quantify this relationship, Krannitz *et al* (*26*) determined nicotine dependence by the cotinine urine test in patients undergoing Austin bunionectomy, and found that as urine cotinine level increased, the healing time also increased ($p < .01$).

CONCLUSION

Smoking has significant effects on the chance of union in fracture healing particulary in tibial shaft fractures, spinal and foot and ankle fusions. The delay in union is more apparent in those cases requiring bone shafts, as there is an increased chance of devascularising the graft. Smokers have a 40% increased time to union and chance of nonunion compared with non-smokers. We recommend that patients should attempt smoking cessation therapy before consideration for elective orthopaedic treatment.

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