CHAPTER **50**

THE EFFECT OF SMOKING ON BONE HEALING

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INTRODUCTION

Cigarette smoke is a mixture of gaseous and particulate matter. Greater than 4,700 chemical compounds have been isolated in cigarette smoke, over 60 of which are known carcinogens.[1] Smoking is the leading avoidable cause of morbidity and mortality in the US.[2] It is also known to be strongly associated with ischemic heart disease and acute coronary events. Smoking is implicated in lung diseases such as cancer and chronic obstructive pulmonary disease, used to describe both chronic bronchitis and emphysema. There are also well-documented effects on wound and bone healing.

Cigarette smoke has 2 phases, the volatile phase, which accounts for 95% of the smoke, and the particulate phase.[2] Approximately 500 gases, including nitrogen, carbon monoxide, carbon dioxide, ammonia, hydrogen cyanide, and benzene are released during the volatile phase. Roughly 3,500 chemicals are released in the particulate phase, including nicotine, nornicotine, anatabine, and anabasine.[2] It is primarily the nicotine, carbon monoxide, and hydrogen cyanide that are largely associated with impairment in wound and bone healing.[2]

Nicotine is an odorless, colorless, highly toxic, alkaloid, which is the agent most responsible for addiction to tobacco products.[3] One cigarette contains about 8.4 mg of nicotine.[3] During the burning process, nicotine is aerosolized into tar droplets, delivering an average of 1.6 mg per cigarette. Inhaled tobacco smoke reaches the alveoli of the lungs, where 82-92% of nicotine is absorbed. This nicotine distributes rapidly to brain and heart tissues, reaching the central nervous system within 20 seconds of inhalation.[3] Once in the circulation, it causes the release of catecholamines, resulting in vasoconstriction and decreased tissue perfusion. Fibroblasts nonspecifically bind to nicotine, causing an alteration in collagen synthesis and protein secretion. Prostacyclin and prostaglandin I_2 production are decreased. Nicotine has also been shown to inhibit the function of red blood cells and macrophages.[2,3]

Carbon monoxide, which binds to hemoglobin to form carboxyhemoglobin, comprises 4% of cigarette smoke.[1] Smokers can have levels of carbon monoxide up to 40 times that of non-smokers.[1] The net effect is tissue hypoxia, as hemoglobin has a much greater affinity for carbon monoxide than for oxygen.[1,2] Therefore, the oxygen-carrying capacity of the blood is significantly reduced. Hydrogen cyanide inhibits cellular respiratory enzymes, affecting oxygenation at the cellular level. The net effect of these substances is vasoconstriction and diminished oxygen perfusion at the wound site.[1-3]

WOUND HEALING

It is well known that smoking has adverse effects on wound healing. A review by Leow and Maibach analyzed many studies which showed decreased cutaneous blood flow in subjects exposed to nicotine or cigarette smoke.[4] Jensen et al demonstrated a decrease in the subcutaneous tissue oxygen tension in subjects after smoking cigarettes.[5] Mosely and Finseth postulated that the vasoconstriction and increased blood levels of carbon monoxide caused by smoking could impair wound healing, particularly in the extremities.[6] They also noted that severe digital vasoconstriction can occur after smoking a single cigarette. They later conducted a study on rabbits, which demonstrated increased systemic nicotine resulted in decreased wound healing.[7] Forrest et al examined skin flaps from rats, which showed reduced capillary blood flow and distal perfusion in those rats that were given high doses of nicotine.[8] They further demonstrated that when nicotine was withheld for 2 weeks prior to surgery, the hemodynamics of the skin flaps returned to near normal levels. Abidi et al performed a study on active smokers and smokers not allowed to smoke during the perioperative period after open reduction and internal fixation of calcaneal fractures, with regard to healing of the lateral incision.[9] Although the difference was not statistically significant in this study, the authors noted that the patients who continued to smoke throughout the perioperative period had prolonged wound healing times.

It has also been shown that epithelial regeneration and the proliferation of cells within the extracellular matrix are decreased by nicotine and carbon monoxide. Jorgensen et al showed that collagen synthesis was

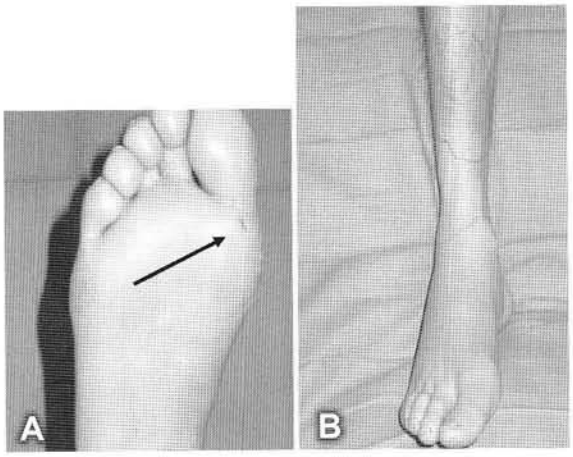

Figure 1A. Shows point of entry of rusty nail beneath the first metatarsal head 8 days prior. B. Presented to emergency room with painful erythematous, edematous right lower extremity. Noted on examination to be particularly taut over the first interspace.

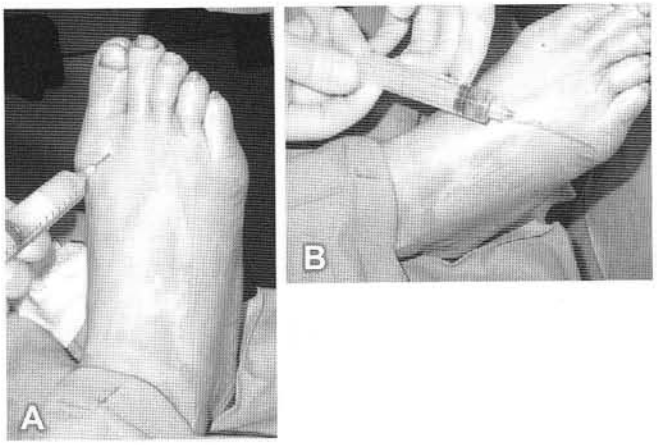

Figure 2A. The technique used to obtain an aspirate from within the first interspace. B. 2cc of fluid was obtained and sent for Gram's stain as well as culture and sensitivity.

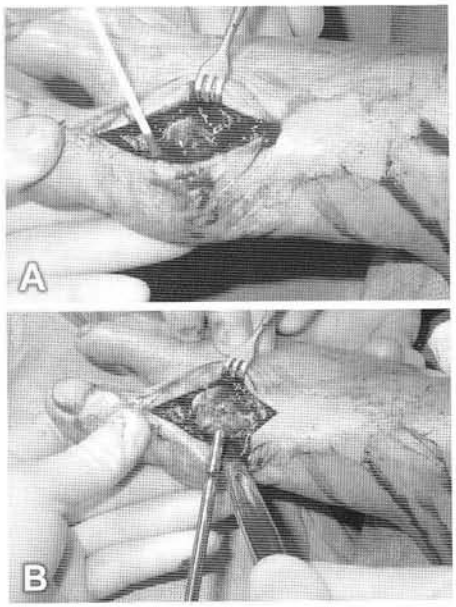

Figure 3A, B. Cultures and bone biopsy samples were taken intra-operatively. The bone biopsy sample was taken to measure the extent of the infection, and to guide the duration of antibiotic as well as surgical therapies.

antibiotic with pseudomonas coverage would be a necessity. Duration of antibiotic use varies depending on the clinical situation; however, soft tissue infections typically require 3-4 weeks of therapy with more extensive osseous infections requiring 6-8 weeks of therapy.[2]

In the event of prior surgeries and in the presence of implanted materials, the implants should be removed and future surgery planned following the appropriate antibiotic course.[3] Surgical drainage may be required in the presence of poor clinical response to antimicrobial therapy. There has been evidence that arthroscopic drainage allows visualization of joint tissue and effective lysis of adhesions with reduced healing and rehabilitation times;[2] however, traditional debridement remain the mainstay of therapy.

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hindered in the wounds of smokers.[10] Mature collagen is the main determinant of the tensile strength in a healing wound, and its assembly depends on sufficient perfusion and oxygenation. This interference with the natural wound healing process may lead to higher rates of postoperative infections in smokers. Thalgott et al conducted a retrospective study for patients with postoperative spinal wound infections.[11] They found that 90% of patients who sustained an infection following elective spinal fusion were smokers. The authors concluded that smoking is a controllable variable that should be stopped in the perioperative period.

BONE HEALING AND NONUNION

In addition to the profound effects on soft tissues and circulation, smoking is also believed to retard the healing of bone. De Vernejoul et al demonstrated that smoking impairs osteoblast function in osteoporotic bone.[12] The quantity of bone remained normal, but the rate of bone formation was decreased. Campanile et al suggest that the effects of smoking are mediated by the vasoconstrictive and platelet aggregating properties of nicotine, the hypoxia promoting effects of carbon monoxide, and the inhibition of cellular respiratory enzymes by hydrogen cyanide.[13]

Numerous animal studies have shown the adverse effects of nicotine on bone healing, with increased rates of delayed or nonunion, inhibition of revascularization of bone graft, and increased rates of pseudarthroses of spinal fusions. Brown et al performed a retrospective study that showed a pseudarthroses rate five times greater in smokers versus non-smokers undergoing lumbar spinal fusion.[14] Cobb et al found smokers to have a relative risk of nonunion 3.75 times greater than non-smokers after an ankle arthrodesis.[15]

In a study by Ishikawa et al, the rate of nonunion was examined in patients receiving rearfoot fusions between smokers, non-smokers, and smokers who quit prior to surgery.[16] The nonunion rate in smokers was 18.6%, as compared with 7.1% in non-smokers. Patients who had ceased smoking prior to surgery were 11.1%. These figures strongly suggest that smoking has detrimental effects on the healing of rearfoot fusions. The time interval that must pass after cessation of smoking before beneficial effects on the rate of nonunion is unclear. Campanile et al note suggestions that range from 1 day to 3 weeks preoperatively and from 5 days to 4 weeks postoperatively.[13] Sherwin recommends smoking cessation at least 12 hours prior to surgery, allowing the body to clear itself of carbon monoxide.[17] Whitesides et al recommend abstinence from smoking for 60 days prior to elective spinal surgery.[18] They base this suggestion on studies showing that a nonsmoker can make 1 cm of bone in 2 months, whereas it takes a smoker an average of 3 months to produce the same amount of bone. Studies on smoking cessation and improved wound healing outcomes recommend abstinence ranging from 5-12 days preoperatively.

LABORATORY TESTING

Benowitz et al showed that self-administration of nicotine is driven by the need to maintain serum nicotine concentrations.[19] Smokers or smokeless tobacco users self-titrate tobacco use to achieve steady-state venous concentrations in the range of 30-50 μg/L, with the full range seen in the majority of tobacco users being 5-100 μg/L.[2] As smokers consume cigarettes during the day, nicotine accumulates in the blood, reaching a plateau averaging 40 μg/L throughout the day.

Nicotine has an elimination half-life of 2 hours. Nicotine metabolism occurs predominantly in the liver via the cytochrome P450 system, with small contributions from the lung and kidney.[2] Once entering the liver, about 70% of nicotine exits in the form of metabolites, with 30% exiting unchanged. Physiological events such as eating, posture, and exercise, which reduce hepatic blood flow, reduce the rate of nicotine metabolism. Renal clearance of unmetabolized nicotine depends largely on urinary pH and can account for 2-35% of nicotine excretion.[2] Some nicotine is reabsorbed in the proximal tubules, where the pH is higher. Renal clearance accounts for 10-15% of the direct elimination of nicotine, with 17% eliminated as cotinine in the urine.

Approximately 70% of circulating nicotine is metabolized to cotinine. Smokers tend to maintain cotinine blood concentrations ranging from 250-350 μg/L.[2] Cotinine has an average half-life of 20 hours and has no apparent direct pharmacologic action. Anabasine and nornicotine are tobacco alkaloids present in tobacco products. Nornicotine is also a nicotine metabolite. Virtually all tobacco products contain these alkaloids, therefore the presence of these alkaloids in biological fluids indicates active tobacco use. It should be noted that anabasine and nicotine metabolites are not found in urine specimens from patients using nicotine replacement therapy.[2]

Serum nicotine or urine cotinine concentrations can be used to guide dosage in nicotine patch therapy. Absence of nicotine metabolites or anabasine can be used to document abstinence from tobacco products. Urine concentrations of nicotine and cotinine correlate with cigarette use in active smokers.[2] According to Lawson et al, the urine output of cotinine is proportional to the

number of cigarettes per day or the nicotine patch dose.[20] Riboli et al and Haufroid and Lison found that urine cotinine >50 µg/L consistently differentiated abstinence from continued tobacco use.[21,22] With these laboratory tests available, physicians may utilize random testing to verify compliance from patients prior to and after surgery. This helps the surgeon optimize the patient's bone and wound healing capabilities and minimizes the risk of nonunion. It is important for the physician to come to an agreement, or contract, with the patient regarding abstinence from tobacco during the preoperative and postoperative periods. Included should be a signed document by both the physician and patient, as well as results of the above mentioned laboratory tests.

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