A REVIEW PAPER

Cigarette Smoking and Its Orthopedic Consequences

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ABSTRACT

Cigarette smoking and its ramifications are coming under increasing scrutiny in the field of orthopedic surgery. Smoking has been implicated in impeding bone metabolism and fracture repair, and increasing the rate of postoperative infection and the incidence of nonunion. This article reviews the current body of knowledge on these topics, as well as the potential adverse effects of smoking on wound healing and microsurgical procedures. An in-depth discussion on the pathophysiologic mechanisms of nicotine is also included.

While public health efforts have mainly focused on the effect of cigarette smoking and nicotine on the risk for cancer and heart disease, increasing attention is being paid to their effect on the musculoskeletal system. Clinical observations suggest that smoking interferes with wound healing and bone repair. Orthopedic surgeons should be aware of the potential harmful effects of smoking and should alert patients to these dangers.

SMOKING AND WOUND HEALING

It is well known that smoking has significant and multiple effects on blood circulation. Smoking can increase heart rate, total peripheral resistance, blood pressure, cardiac output, and coronary blood flow.[1-9] Studies have repeatedly demonstrated that smoking also impairs blood flow in the systemic microcirculation.[10-12] Because of these reports, surgeons have suspected that patients who smoke cigarettes have a higher incidence of vaso-occlusion after surgery and problems with wound healing. For example, Mosely and Finseth[13] showed that after microvascular repair, the perfusion status of replanted digits is significantly impaired in smokers. Smoking has also been shown to increase the need for amputation due to arterial occlusive disease[14] and to increase the rate of complications, poor outcome, and reamputation after leg amputation.[15,16] Pohjolainen and Alaranta[16] showed that male smokers with below-the-knee amputations due to vascular problems walked more slowly and for shorter distances than nonsmokers.

Smokers have also been shown to have a higher rate of failure of skin flaps and arteriovenous shunts.[17] Experimental and clinical studies in the plastic surgery literature have yielded similar results by showing increased flap necrosis in smokers who have undergone vascularized-pedicle skin flaps.[18-23] A strong association between passive smoking and development of Legg-Calvé-Perthes disease has also recently been proposed, probably due to nicotine further restricting the tenuous blood supply to the femoral head.[24]

The negative effects of cigarettes have been hypothesized to be due to an increase in platelet aggregation.[25-27] Some of the gaseous by-products from tobacco smoke, such as hydrogen cyanide and carbon monoxide, have also been implicated.[28] Hydrogen cyanide inhibits respiratory enzymes and may exert deleterious effects on wound healing by inhibiting oxidative energy metabolism at the cellular level.[13] Nolan et al,[18] in a study examining the acute effects of cigarette smoke on skin flaps in rats, found that carbon monoxide binds to hemoglobin with a higher affinity than oxygen, resulting in a reduction in the oxygen-carrying capacity of hemoglobin. This, in turn, decreases the availability of oxygen by producing a shift to the left in the oxyhemoglobin dissociation curve, which results in a decrease in oxygen release at the tissue level.

Both laboratory experiments and epidemiologic findings indicate that nicotine, rather than gaseous by-products, is the most detrimental constituent in

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cigarettes in relation to wound repair and skin-flap viability. Nicotine has been shown to inhibit cellular proliferation and the production of epithelial cells.[29-31] Mosely and Finseth[30] believe that nicotine's vasoconstrictive effects in cigarette smoke may increase skin necrosis in rats exposed to smoke after surgery. Other researchers support this conclusion by demonstrating that nicotine treatment alone significantly decreased skin flap survival in rats and pigs.[31] More importantly, Sachar et al[32] showed that nicotine has detrimental effects on microvascular patency and survival of ischemic limbs. Their data suggest that the adverse effects of nicotine may be due to both long-term microvascular changes and short-term vasoconstrictive effects, and recommend smoking cessation after digital reimplantation.

Others support the view that smoking after reimplantation should be discouraged to optimize circulation. Using laser Doppler flowmetry, van Adrichem et al[33] demonstrated a 19% reduction in blood flow in smokers compared with a 4% increase in blood flow in nonsmokers, after all subjects had smoked 2 cigarettes. The blood flow values did not recover by 10 minutes after smoking. They also noted a long-term effect of smoking, since the mean basal (before smoking) blood flow was lower for the smoking group.

Despite all of this evidence, whether cigarette smoking is a risk factor for poor outcome for a microvascular free flap continues to be controversial. Khouri,[34] in a prospective, double-blind, randomized clinical trial, conducted a survey of 495 microvascular free flaps to determine the most current practice patterns and outcomes. Of the risk factors, obesity, peripheral vascular disease, and radiation to the recipient area appeared to be associated with an increased incidence of failure and complications, while smoking had no effect. Thus the detrimental vasoconstrictive effect of nicotine in clinical practice may not adversely affect the success rate of certain orthopedic procedures when performed by technically skilled and experienced surgeons.

SMOKING AND BONE METABOLISM

Other concerns for the orthopedic surgeon are the detrimental effect of smoking on bone metabolism and on the relationship between smoking and osteoporosis. Tobacco smoking has been suggested as a risk factor for osteoporosis.[35-39] Postmenopausal women who smoke lose significantly more cortical bone and have more spinal osteoporosis than nonsmoking women.[40-48] de Vernejoul et al[35] showed evidence that the mechanism may be due to tobacco smoke directly interfering with osteoblastic function and decreasing bone formation. Tobacco smoke extracts have also been reported to induce calcitonin resistance,[49] which has been hypothesized to contribute to the development of primary or secondary osteoporosis and increase bone resorption at fracture ends.[50]

Several studies have looked exclusively at the relationship between cigarette smoking and bone mineral density (BMD). The use of smokeless tobacco and tobacco smoke extracts have been associated with alveolar bone loss.[51,52] Rundgren and Mellstrom[53] examined the relationship between bone mineral content (BMC) and cigarette smoking and found that the mean values of BMC for smokers compared with nonsmokers were, for men, approximately 10% to 20% lower, and for women, 15% to 30% lower, in all age groups studied. Others have shown a difference in BMD of lumbar vertebrae and proximal femora when comparing smoking and nonsmoking identical twins.[43] They concluded that changes in BMD increased the risk of fractures in men and women smokers two to six times that of nonsmokers. In 1993, Broulik and Jarab[54] implicated nicotine as possibly having long-term effects on bone metabolism. They showed a significant reduction of BMD and BMC in nicotine-treated animals compared with that in animals without nicotine.

SMOKING AND LOW BACK PAIN

The influence of cigarette smoking on the prevalence of low back pain is coming under increasing scrutiny. In many epidemiologic studies, smoking has been identified as a risk factor for low back pain.[55-63] Frymoyer et al[57] documented a dose-effect relation between the frequency of back trouble and the number of cigarettes smoked or the length of smoking history. Most recently, in a survey of 550 individuals using a validated low back pain epidemiology questionnaire, Hanley et al[64] found a strong correlation between cigarette smoking and back pain as a result of an injury at work. Results showed that one in two smokers experienced back pain as a result of a work-related injury versus one in five for nonsmokers. Moreover, the number of cigarettes smoked per day seemed to have an effect on activity level related to back and leg pain. Of the population of smokers with back pain, subjects who smoked more than a pack per day reported feeling more handicapped by their back pain.

Other studies assessing the correlation between smoking and low back pain have yielded somewhat different findings.[65-67] Boshuizen et al,[68] in a study

comparing the prevalence of low back pain among smokers and nonsmokers, concluded that pain in the extremities is more frequently observed and more clearly associated with smoking than pain in the upper or lower spine. This somewhat surprising finding suggests that there may be a general influence of smoking on pain perception, but does not implicate this as a major cause of pain in the back. Other researchers have shown that smoking may actually relieve symptoms of generalized pain by increasing endorphin levels.[69] This has lead to the speculation that the soothing effect of endogenous opiate release from smoking may be a reason why people smoke, especially in stressful situations.[2]

Thus the association between smoking and low back pain remains unclear, and the mechanism for this possible correlation remains an enigma. One theory is that microfractures in the trabeculae of the lumbar vertebral bodies are caused by osteoporosis due to smoking.[70] Another theory is that the effects of smoking are mediated through cough symptoms.[59] Several studies have shown that a chronic cough was the most frequently reported symptom linking smoking and back pain.[59,61,63] Coughing is believed to increase intra-abdominal pressure and therefore intradiscal pressure, putting increased mechanical stress on the spine.[61,64] The cough, however, may not be necessarily directly related to smoking, since some researchers have not found positive correlations among coughing or smoking, and back pain,[64] while others have stated that the cough alone does not explain the association of smoking with back pain.[59] Deyo and Bass[59] have proposed that smoking may simply be a marker for a complex combination of social traits that are associated with increased risk of back pain, such as physical job demands, life stress, and other health habits.

There has also been some recent evidence that smoking apparently alters the metabolism of the intervertebral disc, making it more susceptible to mechanical failure and thereby a source of pain. Battie et al[71] performed a magnetic resonance imaging study of intervertebral discs on identical twins with discordant smoking habits. Results showed that disc degeneration scores were 18% higher in the lumbar spines of smokers compared with nonsmokers. The authors proposed that vascular changes as a result of arteriosclerotic plaques in subjects who smoke may negatively affect blood supply to the disc, thus affecting disc nutrition. This theory was also supported by Mooney et al,[72] who have shown that injecting an amount of nicotine equivalent to that found in one cigarette into the blood stream of dogs causes a reduction in vertebral body blood flow. Holm and Nachemson[65] have presented a similar hypothesis suggesting that smoking decreases the solute-exchange capacity in the intervertebral disc and reduces the circulation outside of the disc.

These findings on the influence of smoking on the intervertebral disc correlate well with the clinical experiences of others. Hanley and Shapiro[73] reported on a follow-up of 120 patients who had undergone primary excision of a lumbar disc at a single level for radicular symptoms. This study showed a strong association between a long history of cigarette smoking and disabling low back pain after an operation on the vertebral disc. Results indicated that one of the main factors predisposing a poor outcome from the operation included a history of more than 15 pack-years (defined as an average of one pack a day for 15 years) of cigarette smoking and emphasized the need to properly select patients who would most benefit from such a procedure. Kelsey et al[74] and Heliovaara and coworkers[75] found an increased incidence of herniated discs in patients who smoked cigarettes. These studies suggest that a history of smoking should be one of the factors to consider when deciding whether to perform a surgical procedure for lumbar disc herniation, especially if present with other negative predictive factors for a successful outcome, such as prolonged symptoms, a compensable work situation, and age >40 years.[76]

SMOKING AND POSTOPERATIVE INFECTION

Although the scientific evidence is sparse, several series have implicated smoking as a significant risk factor for postoperative infection.[77] In a study by Kayvanfar et al[78] on wound infections after instrumented posterolateral adult lumbar spine fusion, significant predisposition for infections was found in obese patients and in patients who smoked. Taylor et al[79] and Thalgott and coworkers[80] have noted greater infection rates in this patient group, as well as in malnourished patients. Thalgott et al found that 90% of patients who sustained a postoperative infection after elective surgery were cigarette smokers. Because of these findings, some orthopedic surgeons now mandate complete abstinence from nicotine for a period of time before surgery, although the exact amount of time required is unclear.[81]

SMOKING AND NONUNION

Research on whether smoking may affect fracture repair has also been limited. In an animal study to investigate the relationship between ciga-

rette smoking and fracture healing, Lau et al[50] found the incidence of nonunions or delayed unions in cigarette smokers to be twice that of nonsmokers. Schmitz and colleagues[82] showed clinical evidence that smoking may be implicated in nonunions of diaphyseal fractures resulting from trauma. In 1993, they treated 200 consecutive closed and grade I open tibial shaft fractures in smokers and nonsmokers with either cast immobilization, intramedullary nails, or external fixation and demonstrated that smoking may delay healing. Radiography revealed a 43% delay in healing in the smoking group, and the average time to complete union was 70% longer in smokers compared with nonsmokers. Blanks et al[83] demonstrated a decrease in bone-healing strength in rats treated with a low dose of nicotine, suggesting that nicotine may be detrimental to fracture repair.

Clinical observations suggest that smoking may also interfere with the healing of bony fusions, yet results of studies attempting to demonstrate an association between smoking and pseudarthrosis are variable. The rate of nonunion or pseudarthrosis in smokers after spinal fusions has been reported to be three to four times higher than in nonsmokers.[84-86] Brown et al,[85] looking at the role of cigarette smoking in the development of pseudarthrosis after two-level laminectomy and fusion in 100 patients in a case-control study, found that pseudarthrosis occurred in 20 of the 50 smokers, for a 40% rate, whereas only 4 of the 50 (8%) nonsmokers developed this complication. Hanley and Levy,[86] in a review of 50 cases of fusion for lumbosacral spondylolisthesis, showed that smoking was associated with poor outcome, but not to a statistically significant degree. Brodsky et al,[87] in their review of 34 symptomatic cervical pseudarthroses, could find no association with smoking. Cobb et al[88] examined cigarette smoking and nonunion after ankle arthrodesis and reported results showing the relative risk of nonunion increased 3.75 times for smokers versus nonsmokers. Unfortunately, most of these retrospective studies were not well controlled for certain confounding variables, such as occupation or socioeconomic status, nor did they define a pathophysiologic mechanism.

Recently, some researchers have proposed that systemic nicotine from cigarette smoke may be the most important constituent in smoke affecting bone nonunion. Daftari and colleagues[89] demonstrated that nicotine decreases revascularization of bone graft placed in the anterior chamber of the rabbit eye. Although the biologic environment of the spine is different from that found in the eye, they concluded that inhibition of early revascularization by nicotine is the pathophysiologic mechanism by which smoking adversely affects the healing of spinal fusions. In an in vivo study in rabbits undergoing single-level lumbar posterior lateral intertransverse process fusion using autologous iliac bone graft, animals that received nicotine went on to nonfusion, while, of those that did not receive the drug, 56% were judged to have solidly fused lumbar spines.[90] Using the same animal model, Boden et al[91] confirmed this finding by showing that the inhibitory effects of nicotine on spinal fusion can be overcome by using an osteoinductive bone protein extract. These experiments have been instrumental in implicating nicotine in delaying bone union and further establish the relationship of the harmful effects of tobacco on bone.

PHARMACOLOGIC EFFECTS OF NICOTINE

Although the precise mechanism by which nicotine acts adversely on bone and soft-tissue healing remains unclear, many theories exist. Nicotine has been shown to be the most vasoactive compound in tobacco smoke or in smokeless tobacco. Nicotine may act on the vasculature by constricting the microcirculation, which decreases blood supply to the target organ,[3,17] or nicotine itself may directly affect the physiology of the end organ.

Among the vasoactive theories there are several hypotheses. Nicotine may indirectly increase or decrease hormone release or may act directly on the nicotinic receptors of the sympathetic ganglia. Nicotine has been shown to inhibit the synthesis of prostacyclin in rabbit aorta and human peripheral veins.[92,93] This in turn reduces prostacyclin's effect on platelet antiaggregation and its vasodilating actions, thus causing increased vasoconstriction and platelet activation, which may lead to vascular thrombosis.

Nicotine's main pharmacologic action may also be exerted through the production of catecholamines, which promote peripheral vasoconstriction.[2,18] Epinephrine and norepinephrine have been shown to be released from the adrenal medulla in response to circulating nicotine.[94-97] These hormones in turn may be responsible for the peripheral vasoconstrictive effect of nicotine at the end organs and peripheral smooth muscles. This theory is supported by work suggesting that the precapillary vessels, which are sparsely innervated, are quite sensitive to vasoactive agents.[97] Wigoda et al[98] have demonstrated that the vasoactive effects of smoking are probably due to the nicotinic effects on sympathetic fibers at the gan-

glionic level or the postganglionic nerve fiber. By measuring relative digital blood flow before and after a digital sympathetic block in subjects who were regular smokers, they were able to show that provision of a local anesthetic transmission block along the path of the nerve reverses the decreased blood flow that occurred after smoking.

The intense vasoconstrictive effect on the microvasculature caused by nicotine may inhibit the angioblastic response during revascularization in the healing bone.[89] Angiogenesis has been shown to be an essential part of normal growth and repair.[99] If nicotine's effect on bone repair is primarily due to its effect on the angiogenic process, it may decrease success in treating conditions in which an augmented vascular supply is needed, such as wound healing, organ ischemia, burns and fracture repair. Natural bone healing is optimized by maximal ingrowth of fibrovascular stroma in the early stages of fracture repair.[100] Blood supply and appropriate stimuli of angiogenesis are therefore crucial.[101-103] Rhinelander et al[104] demonstrated that periosteal neovascularization of the fracture site is most important. Nicotine's ability to discourage the growth of new blood vessels in bone has broad implications for the treatment of many orthopedic ailments, such as high-risk fractures, pseudarthrosis, bone grafts, osteomyelitis, aseptic necrosis, arthrodesis, and osseous defects.

Nicotine may also affect bone metabolism by directly affecting osteoblasts themselves. Several reports have shown that nicotine given in toxic doses can delay ossification of vertebrae and limbs during fetal development.[105-107] In 1991, Fang and colleagues[94] concluded that nicotine suppresses cellular proliferation and stimulates alkaline phosphatase activity (a marker of osteoblast function) in osteoblast-like cells in a dose-dependent manner, supporting evidence of nicotine's direct effect on bone cells. Ramp and colleagues[108–110] found that nicotine may also interfere with the cellular processes of chick embryo osteoblasts. In one study, they found that nicotine and smokeless tobacco extract both stimulated glycolysis and inhibited bone collagen synthesis and mitochondrial activity in cultured embryonic chick tibiae.[110] In osteoblast-like cells isolated from chick calvariae, nicotine inhibited release of alkaline phosphatase activity to the medium, and inhibited hydroxylation of [^{3}H]proline (an index of collagen synthesis).[108]

Although their reports of nicotine's effect on alkaline phosphatase activity were in contrast to those of Fang et al,[94] these differences could potentially reflect variations in cell culture conditions, species differences, and type of osteoblast model used, degree of cell confluence, form and concentration of nicotine studied, or interactions of nicotine or its metabolites with factors in the medium. The concentrations of nicotine that were studied in these experiments were about the same as or higher than the mean steady-state serum concentrations of nicotine reached by habitual cigarette smokers (0.06 to 0.3 μmol/L)[111] and the concentrations of nicotine found in the saliva of chronic snuff users (0.6 to 9.6 μmol/L).[26] Because only very high doses of nicotine affect osteoblasts, adverse effect on bone repair may also be due to decreased microvasculature and bone perfusion.

PRE- AND POSTOPERATIVE INTERVENTION

The results of these studies suggest the need for smoking cessation before an orthopedic operative procedure. But how long does a surgeon wait after the patient has stopped smoking to perform a procedure such as fusion? No data currently exist for answering this question.

Studies recommend that patients not use tobacco anywhere from half a day to 1 week before surgery. Rees's[112] minimum of 12 hours is based on the amount of time it takes to clear carbon monoxide from the blood and return the carboxyhemoglobin to normal. Others have suggested 1 week, based on the half-life of free radicals and thrombotic components in tobacco.[15] After surgery, it would be further advisable to recommend continued cessation of smoking for at least a week based on Mosely and colleagues'[30] experimental data showing that nicotine can impair wound healing for up to 10 days after incisions are created. Smoking in the immediate postoperative period has the potential of converting a marginal circulatory deficiency into a wound disaster and, therefore, should be avoided.

In addition to the acute and subacute effects of smoking, one must also take into account its long-term effects. Perhaps smoking cessation, although it may prevent further damage, may come too late to reverse adverse effects.[81]

CONCLUSION

Cigarette smoking continues to be recognized as one of the major causes of preventable disease in the United States. An increasing body of evidence suggests that nicotine and smoking have adverse consequences on bone metabolism and bone repair. Prospective orthopedic patients should be questioned regarding their smoking history, particularly when an elective procedure is being contem-

plated, and there is time to abstain from smoking before surgery.[28] The potential adverse effects of smoking on bone should be discussed when the orthopedic surgeon conveys the prognosis for any surgical procedure.

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