

Nicotine Replacement Therapy in Head & Neck Microvascular Reconstruction

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Abstract

Head and neck cancer patients requiring microvascular free flap reconstruction are likely to have a recent or active smoking history. Nicotine replacement therapy (NRT) is an option during their hospital stay but sparse evidence exists of its clinical effects. We review the current literature on nicotine replacement therapy (NRT) in microvascular free flap reconstruction. A thorough literature review was conducted using PubMed, analyzing articles relevant to the subject matter. Various search terms were used to identify articles regarding nicotine, nicotine replacement therapy, microvascular anastomosis, and wound healing. Smoking has been shown to have a negative effect on wound healing. Nicotine, however, has opposing effects on the wound healing process. Studies have shown low dose nicotine increases factors related to wound healing like angiogenesis, while high concentrations of nicotine impair these same processes. The two studies using nicotine in microvascular anastomosis animal models demonstrated decreases in flow and anastomotic patency when exposed to nicotine. While no human trial exists, nicotine has been shown to reduce microvascular anastomosis flow and patency rates. Therefore, NRT should be avoided in microvascular free flap patients.

Keywords: Nicotine; Microvascular surgery; Head; Neck reconstruction

Introduction

Cigarette smoking is an established risk factor for head and neck cancer. Patients who undergo a surgical intervention may choose to continue smoking up until the date of surgery which has been shown to have negative effects on wound healing in the post-operative period [1]. In clinical studies, there is a significantly higher incidence of tissue flap necrosis in smokers after breast and plastic/reconstructive surgery [2]. Therefore, smoking cessation is encouraged in the pre-operative period to improve wound healing in the post-operative period. Nicotine stimulates nicotinic receptors in the autonomic nervous system

resulting in sympathoexcitatory effects with catecholamine release from nerve endings [3,4]. Addiction to tobacco products is directly related to chronic nicotine exposure. To aid patients in smoking cessation, nicotine replacement therapy (NRT) has become a main treatment option. In the outpatient setting patients have many over the counter options for NRT. Patients in the hospital who are current or former smokers frequently receive nicotine to help withdrawal cravings during their hospital stays. Nicotine given alone eliminates many of the damaging free radical products smoking produces. Studies on the effects of smoking have demonstrated negative effects on wound healing. While very few controlled studies exist, smoking is observed to cause a greater rate of skin flap necrosis and delayed wound healing [5]. The effect of nicotine on wound healing has yielded wide-ranging results. Animal studies have shown increased intestinal and muscle blood flow with nicotine but decreased peripheral perfusion [6]. Yaffe et al. [7] exposed rats to cigarette smoke who underwent femoral artery end-to-end anastomosis as an experimental model. They found no difference in anastomotic patency between experimental and control groups [7]. However, the effects of nicotine replacement on patients undergoing head and neck microvascular reconstruction has not been studied and a review on its use is missing from the current literature. This review seeks to provide the reconstructive surgeon with a summary of pertinent literature related to the use of nicotine replacement in the care of these patients. As the success and failure of microvascular reconstruction is multifactorial and only a small number of variables have been studied, this manuscript suggests another controllable factor in enhancing surgical outcomes.

Materials and Methods

In order to explore pertinent literature related to the subject at hand, PUBMED searches were performed using the search terms "nicotine," "microvascular," "head and neck reconstruction," "anastomosis," "wound healing" and various combinations of the mentioned terms. Review articles pertinent to the subject were studied by multiple authors, and the highest quality studies were included for review in this manuscript after

being vetted by all participating authors. Relevant information was gleaned and used in the preparation of the manuscript

Results

Effect of nicotine on wound healing

While smoking has clearly been showed to negatively affect wound healing, the effect of nicotine alone requires a more in-depth analysis. Wang et.al showed that in vitro simulation of human endothelial progenitor cells (EPC) with nicotine increases function of these cells promoting new vasculature [8]. However, they also demonstrated a dose dependent effect of nicotine on EPC function showing that doses higher than 10^{-4} molar produce an inhibitory effect. Morimoto et al. [9] in 2007 studied the wound-healing effect of topical nicotine on wounds created in healthy mice. Their data showed concentrations of $10 \mu\text{l}$ of 10^{-4} molar nicotine resulted in smaller wound areas, longer neoeepithelium and larger area of new capillaries compared to a control buffered saline solution [9]. Heeschen et al. [10] studied angiogenesis under hypoxic conditions using the hind limbs of mice where the femoral artery was occluded for a short period to simulate tissue ischemia. Mice were given either locally injected doses or oral nicotine to simulate systemic levels. Systemic administration produced nearly 75% increase in capillary density where local administration produces only a 46% increase [10]. Sorenson has used a variety of human models to simulate wound healing with concurrent nicotine patch use. His studies have shown that nicotine patch attenuates inflammatory wound healing mechanisms but induces angiogenesis and collagen synthesis [2]. Thus, current research supports the concept that low levels of nicotine accelerate angiogenesis and wound healing in animal models where as high levels of nicotine reduces peripheral blood flow and wound angiogenesis [8,11]. While there is no evidence that nicotine will improve wound healing in abstaining smokers, there is no evidence to suggest a detrimental effect in head and neck patients [1]. There is still an information gap of nicotine's effects as most studies compare continued smoking versus nicotine in isolation.

Effect of nicotine on microvascular anastomosis

Few studies have been done on nicotine's effect in microvascular reconstruction. Rao et al. [12] in 1983 performed two animal experiments assessing blood flow and patency through a saphenous flap. Rao et al. created an animal model by clamping the femoral artery off and transecting the saphenous artery 2 cm from its origin and then performing an end-to-end anastomosis [12].

Experiment 1

Nicotine was injected into the femoral artery in doses of 0.05 mg up to 14 mg. 30 min after the operation was complete the blood flow through the anastomosis was measured using an electromagnetic flow probe. All grafts were patent at the conclusion of the experiment. Marked vasoconstriction and decrease in mean flow were noted at doses of 1 mg to 8 mg of nicotine. Doses of 4 mg produced 42% decrease in mean flow

and 8 mg doses resulted in a 71% decrease. Higher doses did not reduce flow beyond this maximum point.

Experiment 2

Four groups of 10 animals underwent bilateral femoral artery transection and re-anastomosis. All groups were explored for vessel patency three weeks after surgery. Group 1: no nicotine given to animals. Group 2: intra-peritoneal nicotine was given 2 mg/kg twice daily three weeks pre-operatively and three weeks post-operatively. Group 3: no pre-operative nicotine while 2 mg/kg was given twice daily for three weeks post-operatively. Group 4: nicotine doses of 2 mg/kg given for three weeks pre-operatively and none post-operatively. All control animals with no exposure to nicotine had patent anastomosis three weeks post-op. Pre-operative nicotine and post-operative nicotine alone resulted in a 100% patency rate. Nicotine exposure pre-operatively and post-operatively resulted in two (2/16) occluded anastomoses for an overall patency rate of 87.5%. Sachar et al. [13] in 1997 used rat-knee replantation models to study acute and chronic effects of nicotine on anastomotic patency. Rat knees were removed using the femoral artery and vein as the pedicle and anastomosed to contralateral femoral vessels. Rats were injected with 1 mg/kg subcutaneous nicotine twice daily and compared to control rats with saline injections only. Injections were given 30 days prior to and 10 days post limb transplantation. All donor knees were subjected to either a 4 hour or 6-hour ischemia time. Graft patency was assessed on post-operative day 10. Nicotine grafts subjected to 4 h ischemia time had an 33% patency rate while controls showed a 89% patency rate. Grafts exposed to 6 h ischemia time were found to have 33% patency rate compared to 45% in controls [13]. In all failures both the artery and the vein clotted.

Discussion

Smokers routinely undergo surgical procedures that require inpatient hospital stays. Without the ability to smoke, symptoms of nicotine withdrawal can occur within hours and usually peak in the first week. These include depressed mood, heightened irritability, increased restlessness, difficulty concentrating, increased appetite, sleep disturbance, anxiety and delirium [14]. Additionally, they have the urge or desire to smoke referred to as cravings. It has been shown that NRT delivers nicotine at sufficient levels to alleviate these withdrawal symptoms and aid patients attempts to quit smoking [15]. However, in the hospital the immediate goal is not to quit, but to avoid withdrawal symptoms. To ease these symptoms, hospitals routinely offer NRT options during their inpatient stay. Currently NRT is available in five delivery methods: gum, lozenges, nasal spray, patches, and inhalers. Hospitals typically carry nicotine patches and may have additional delivery methods depending on where one practices. Nicotine undergoes first pass metabolism in the liver reducing the bio-availability of nicotine pills. Therefore, alternate methods of delivery were manufactured including gum, transdermal patches and lozenges. Transdermal patches are available in several different doses and deliver between 5 mg and 52.5 mg of nicotine over 24 h period resulting in plasma levels similar to trough levels seen in heavy smokers [3,4]. Nicotine gum is available in 2 mg and 4 mg strengths while

lozenges come in 1 mg, 1.5 mg, 2 mg and 4 mg strengths. All forms of replacement attempt to replicate the amount of nicotine from cigarettes, which deliver 1-3 mg of nicotine per cigarette. Clinical studies have shown heavy smokers maintain nicotine plasma levels between 8.5 and 38.4 ng/ml [4].

Nicotine's effects on inflammation and angiogenesis and wound healing have been well studied however the mechanism of action is complex and not well understood. Nicotine appears to attenuate inflammation in wound healing while promoting wound proliferation mechanisms such as angiogenesis. However, the effect of nicotine on angiogenesis has is dose dependent. Low doses of nicotine promote angiogenesis and wound healing as Wang et al. [8], Morimoto et al. [9], and Heeschen et al. [10] have shown. However, at higher concentrations of nicotine, the effects begin to negatively affect wound healing. Wang showed these inhibitory effects begin at concentrations above 10^{-4} M. Sorenson has shown that angiogenesis and collagen synthesis improved with a nicotine patch in human wound healing models but the exact dose where nicotine switches from a promoter of angiogenesis to an inhibitor is unknown. A review by Nolan et al of NRT in the perioperative period notes that there is no evidence from human studies demonstrating NRT increases the risk of healing-related or cardiovascular complications [16]. They argue the benefits of smoking abstinence (long term NRT therapy) in the peri and post-operative period mean NRT use should not be discouraged in surgical patients. It is clear more research is needed on the effects of NRT on wound healing in surgical patients. There have been many studies examining smoking as a predictor for flap survival and wound healing [5]. Nicotine in doses equivalent to heavy smokers has been shown to reduce capillary blood flow and viability of random pattern skin flaps in rats [11]. However, nicotine replacement therapy has not been studied in regards to microvascular free flap patients. The two studies that specifically use nicotine in the setting of microvascular anastomosis show clear negative impacts compared to controls. While there is no evidence in human subjects, these two studies show that nicotine decreases blood flow and increases the rate of thrombosis at the anastomotic site.

The use of NRT in the post-operative free flap patient population must weigh the benefits of wound healing and reducing nicotine withdrawal, with the negative effects on inflammation, blood flow, and anastomotic patency. Given that microvascular anastomotic patency is the most important factor in the immediate post-operative period, it is our opinion that NRT should be avoided. In this period symptoms of anxiety, agitation, and delirium are most critical to control. These can be damaging not only to the flap but also prolong their recovery from self-injurious behavior. Evidence for NRT use to aid these specific symptoms in the ICU setting is inconclusive. Therefore, standard pharmacotherapy including benzodiazepines and antipsychotics may be safest during the immediate post-operative period to control anxiety and delirium [17].

Conclusion

Nicotine has been shown to promote wound healing while negatively impacting inflammation, blood flow, and microvascular patency at the anastomotic site. Due to reduced microvascular patency, nicotine replacement therapy is not recommended in microvascular free flap patients in the post-operative period.

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