

A Second Look at Nicotine Replacement Therapy Before Surgical Procedures

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In this issue of *Mayo Clinic Proceedings*, Nolan and Warner¹ review the literature and provide a speculative synthesis on the controversy surrounding nicotine replacement therapy around the time of surgical procedures. Elective operations offer a special opportunity to motivate active smokers to quit. The extensive harms and costs of cigarette smoking, both to the smoker and to the health care system, are well documented.² In contrast, the perioperative consequences of nicotine are less well understood. As a vasoconstrictor, nicotine contributes to tissue hypoxia and adversely affects the cardiovascular system by raising blood pressure and pulse rates. Nicotine negatively impacts maternal and fetal health and has been speculated to be a carcinogen. The use of nicotine replacement therapy has been reported to be associated with increased mortality after coronary artery bypass surgery³ and in critically ill patients hospitalized in medical intensive care units.⁴ Across surgical specialties, a key concern is that perioperative nicotine use might result in failed operations, the need for repeated operation and readmissions, and increased health care costs. The central unanswered question is whether the benefit of nicotine replacement therapy to help patients quit smoking preoperatively outweighs any potential harmful impact on the overall success of the operation.

In their extensive and clearly presented review, Nolan and Warner¹ summarize the literature—including basic science research, results from animal experiments, and clinical data—regarding the impact of nicotine replacement therapy on operative outcomes. The major limitation of their review remains the relatively limited amount of clinical data and human studies on which to draw clear conclusions. Although the deleterious impact of smoking on nonunion of spinal fusions, failed repairs of hip fractures, and wound healing complications after reduction mammoplasty (among many other conditions) has been well characterized in humans, data related to nicotine alone has come mostly from animal models.

Preclinical animal studies suggest that nicotine can impair bone healing and metabolism,⁵ decrease mechanical strength of healing fractures,⁶ adversely impact osseointegration of titanium implants,⁷ contribute to flap ischemia and necrosis,⁸ and reduce anastomotic patency in blood vessels.⁹ Intriguingly, a contradictory study suggested that nicotine aids in wound healing.¹⁰ However, many of these studies examined nicotine levels likely higher than those achieved in humans through nicotine patch, gum, or lozenge use. One option is to repeat the studies in animals with lower physiologic concentrations of nicotine. Even better would be to perform the critical human studies that could definitively characterize nicotine's effects.

The authors cautiously conclude that policies prohibiting the use of nicotine replacement therapy perioperatively should be reexamined. The implications of their conclusions on preoperative assessment in particular have worldwide importance because many physicians and hospital systems have not fully embraced the use of nicotine replacement therapy perioperatively. At one end of the spectrum (in support of their conclusions), there is little doubt that nicotine replacement therapy is preferable to patients actively smoking at the time of their operation. The good news from this article is that there is no clear evidence of harm from this strategy.

At the other end of the spectrum is the perspective that the goal should be higher—complete smoking cessation and nicotine abstinence around the time of operation. This is the perspective of plastic and orthopedic surgeons in particular, who are concerned that smoking or the use of any nicotine-releasing products, including patches, vaporizers, or gums, increases the incidence of serious complications after aesthetic, reconstructive, and orthopedic surgical procedures. For this reason, many surgeons refuse to perform elective operations in patients who are smokers or are using nicotine in any form. Some require that smoking and the use of any nicotine-releasing products be completely stopped at least

several weeks before elective surgical procedures and not restarted for a week or more postoperatively. Some surgeons cancel the operation if the results of a test for urinary cotinine (a metabolite of nicotine) on the morning of the procedure are positive.¹¹ This position is supported by strong evidence from animal studies, but the lack of clinical studies might lead some to criticize this decision as anecdotally based practice and an illustration of the need for better data to guide an evidence-based approach.

Most readers will likely agree that nicotine replacement therapy is unlikely to affect anesthetic outcome because there are few reports of any harm in the operating room or immediate recovery in the postanesthetic care area. However, the intraoperative phase is relatively brief in comparison to the preoperative and postoperative periods, and it is unclear whether nicotine poses any longer-term surgical risks. Most readers will also agree that the existing limited data do not document a clear harmful effect of nicotine replacement therapy on surgical outcomes, but some may believe that concluding the opposite, that preoperative nicotine replacement therapy is therefore safe, might be premature. The absence of reported harm in limited studies is not convincing proof of safety, and this issue requires further research.

Ideally, the primary role of nicotine replacement therapy in the hospital setting would be to help smokers who have already undergone emergency surgical procedures control their postoperative cravings for cigarettes and to serve as the bridge to lifelong cessation. Hopefully, the recently completed operation will prove to be the final procedure in the patient's lifetime. However, although nicotine replacement therapy is welcome in active smokers hospitalized immediately after emergent procedures, it would be preferable if nicotine replacement therapy has only a temporary role in a larger effort to achieve complete tobacco abstinence.

The elective setting is more complex, and a key principle should be to capitalize on the teachable moment of elective surgical intervention to transition the patient to full tobacco and nicotine abstinence. The difference compared with emergency operations is that there is time to prepare the patient in an outpatient setting through a combination of counseling, quitlines, and medications to help them quit. Existing

policy in England requires that patients scheduled for elective surgical procedures undergo smoking cessation counseling for several weeks preoperatively.¹² Naturally, the ideal is for patients to taper off both smoking and nicotine replacement therapy in the days leading up to the operation and not resume use postoperatively.

Additional studies to characterize the therapeutic nicotine dose response and to convincingly document that nicotine replacement therapy does not affect wound healing, bone fracture healing, or anastomoses would be ideal. Research has revealed that the incidence of wound healing complications in smokers is dose dependent, with higher preoperative cotinine levels linked to a greater risk of healing delay.¹³ Until these nicotine replacement studies are completed, one alternative is to prescribe non-nicotine therapies such as varenicline or bupropion to aid perioperative smoking cessation. The contraindications should be noted, and the adverse effects and efficacy of these medications in this setting should also be studied. Others might question whether to use electronic cigarettes without nicotine (placebo), which have been found to be almost 60% as effective as electronic cigarettes containing nicotine in promoting cessation.¹⁴ However, this approach would not work everywhere, including England, where the use of electronic cigarettes perioperatively for smoking cessation has been discouraged.

Another current challenge is to develop a new assay to distinguish a patient who is actively smoking from one who is using nicotine replacement therapy; in both groups, urinary cotinine levels will be elevated. New tests for anabasine or other metabolites specific to the nicotine from cigarettes will help prevent cancellation of an operation on the day of the procedure for a patient who is compliant with nicotine replacement therapy and has stopped smoking,¹⁵ as opposed to someone who is still smoking and not being honest about his or her tobacco use.

In the final analysis, the goal is to help our patients stop smoking and to utilize the teachable moment of elective surgical procedures as an opportunity to break the addiction to nicotine and achieve permanent smoking cessation. A new diagnosis of myocardial infarction or lung cancer requiring surgical intervention can be one

of the most powerful motivators for a patient to finally quit smoking. Some will question whether allowing nicotine replacement therapy delivers a mixed message to patients that indirectly condones both nicotine addiction and continued smoking. Nicotine replacement therapy should not serve as a bridge to relapse after operation or promote lifelong addiction to nicotine.

Where Nolan and Warner's review succeeds the most is with suggestions of where new research might be directed. The authors note that no animal studies have examined how nicotine may affect surgical site infections, and virtually no human studies have directly examined the impact of nicotine replacement therapy on bone healing, perioperative cardiovascular risk, or plastic surgery wound outcomes. Young surgical researchers in particular could dedicate their careers to answering these questions and to strengthening smoking cessation efforts around the time of surgical treatment. Approximately 42% of surgeons and 72% of anesthesiologists do not routinely counsel patients to stop smoking before an operation or refer them to appropriate cessation services.¹⁶ Increased funding for clinical research on preoperative nicotine replacement therapy will raise awareness of the opportunity to encourage smoking cessation perioperatively and educate frontline clinicians to reduce tobacco's deadly toll across America and worldwide.

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