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Intranasal Nicotine for Postoperative Pain Treatment

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Background: **Despite pharmacological treatment, 70–80% of patients report moderate to severe pain after surgery. Because nicotine has been reported to have analgesic properties in animal and human volunteer studies, the authors assessed the analgesic efficacy of a single 3 mg dose of nicotine nasal spray administered before emergence from general anesthesia.**

Methods: **The authors conducted a randomized, double blind, placebo controlled trial of 20 healthy women (mean age 45 (SD 8) yr) who were to undergo uterine surgery through a low transverse incision. After the conclusion of surgery but before emergence from general anesthesia, the anesthesiologist administered either nicotine nasal spray or a placebo. Numerical analog pain score and morphine utilization and hemodynamic values were measured for 24 h.**

Results: **The patients treated with nicotine reported lower pain scores during the first hour after surgery (peak numerical analog score, 7.6 (SD 1.4) *versus* 5.3 (SD 1.6); $P < 0.001$) and used half the amount of morphine as the control group (12 (SD 6) *versus* 6 (SD 5) mg; $P < 0.05$). Patients who received nicotine still reported less pain than those in the control group 24 h after surgery (1.5 (SD 0.5) *versus* 4.9 (SD 1.4); $P < 0.01$). Systolic blood pressure was lower in the group that received nicotine (105 (SD 3) *versus* 122 (SD 3); $P < 0.001$), but there was no difference in diastolic blood pressure or heart rate.**

Conclusions: **Treatment with a single dose of nicotine immediately before emergence from anesthesia was associated with significantly lower reported pain scores during the first day after surgery. The decreased pain was associated with a reduction in morphine utilization and the analgesic effect of nicotine was not associated with hypertension or tachycardia.**

SEVENTY to eighty percent of the 23 million yearly surgical patients in the United States experience moderate to severe pain in the postoperative period despite pharmacological treatment.[1–3] The opioid and nonsteroidal antiinflammatory medications that are commonly used to treat postoperative pain are limited by their side effects. As such, a novel effective analgesic strategy for the treatment of postoperative pain would be useful.

Antinociception from neuronal nicotinic receptor activation has been demonstrated in several animal models and is thought to result from activation of native descending inhibitory pain pathways.[4,5] Studies in both smoking and nonsmoking human volunteers have shown that nicotine has a mild to moderate analgesic effect in experimental paradigms including heat induced pain,[6] cold induced pain[7,8] and pain induced by electrical shock.[9]

Despite the evidence from studies in animals and human volunteers that nicotine has analgesic efficacy and the relative safety and efficacy of the nontobacco related nicotine administration systems that are currently available, the potential analgesic action of nicotine has not been studied in patients during the postoperative period. In this randomized, double blind, placebo-controlled study; we assessed the analgesic activity of nicotine administered in a nasal spray in women after uterine surgery.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

This study was a randomized, double blind clinical trial with a 24-h data collection period. The study was approved by the institutional review board at Columbia University. Written informed consent was obtained from all patients. Women aged 18–50 yr scheduled to have uterine surgery (either myomectomy or hysterectomy) through a low transverse incision were eligible to be included. We chose to only study women in this preliminary study because animal studies have identified gender differences in the analgesic action of nicotine.[10–12] Patients who had smoked during the past year or had preexisting pain syndromes, hypertension, or any history of cardiovascular disease were excluded. All patients were American Society of Anesthesiologists physical status I or II. The patients were instructed before surgery that they would be asked about their pain with a numerical analog score, where 0 = no pain and 10 = the worst pain that they could imagine. All patients had access to morphine with patient-controlled analgesia after surgery and were instructed in its use in the preoperative period. No other medications were given in the preoperative period.

All patients were given a standardized anesthetic as follows: anesthetic premedication administered in the operating room consisted of 1–2 μg/kg fentanyl and 1 mg vecuronium. Anesthesia was induced with propofol 2 mg/kg and succinylcholine 2 mg/kg. After intubation of the trachea, anesthesia was maintained with a fentanyl infusion of 1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and isoflurane was titrated to adequate anesthetic depth by the clinical anesthesiologist, who was not aware of the treatment group. Muscle relaxation was effected with vecuronium. All patients were given dolasetron 12.5 mg prophylacti-

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cally to prevent nausea and vomiting. At the completion of surgery, the anesthesiologist was given an opaque sealed container with either a nicotine nasal spray (3 mg Nicotrol NS; Pharmacia, Peapack, NJ) or saline nasal spray prepared by the research pharmacy according to a random number table. The study drug was administered by the anesthesiologist as three jets in each nostril (3 mg nicotine or an equal volume of saline) at a 45 degree angle after the muscle relaxant was reversed and while the surgeon was closing the fascia.

Five minutes after extubation and every 5 min thereafter for 60 min, the patient was asked to report the pain that they were experiencing with a numerical analog score. A pain report was also obtained at 2 and 24 h. A patient-controlled analgesia pump was inserted into the intravenous circuit before emergence from anesthesia. It was programmed to deliver a dose of 1 mg morphine when the button was pressed with a lockout interval of 6 min and a maximal dose during 1 h of 10 mg. The patient-controlled analgesia pump was also programmed to allow a rescue dose of 3 mg morphine to be administered by a nurse every 5 min with additional 12 mg morphine maximally by this route every 4 h, if the patient reported a pain score greater than 3 of 10. As such a patient could receive 24 mg of morphine as a maximal dose in the first hour. According to the standard patient-controlled analgesia orders at our institution, the rescue dose was not administered by the nurse if the patient had a respiratory rate less than 8 breaths per minute or was determined by the nurse to be oversedated (sedation scale ≤ 3, where 0 = reflexes not present, 1 = reflexes present, does not respond to verbal command, 2 = eyes open to verbal command or response to name, 3 = lightly asleep, eyes open intermittently, and 4 = fully awake, conversant). No other postoperative analgesic medications were used.

Blood pressure was measured with a noninvasive automatic oscillometric blood pressure cuff every 5 min for the first hour (Agilent Technologies, Andover, MA). Heart rate was monitored continuously with a pulse oximeter and electrocardiographic leads and recorded every 5 min for the first hour (Agilent Technologies). All testing was conducted by the same investigator (D.D.). Both the investigator recording data and the nurse administering medication were blinded to treatment group.

The data were analyzed per protocol. Two subjects from whom informed consent was obtained were not studied for postoperative pain. In one case because of a protocol violation in the standard anesthetic the patient was not randomized and in the second case, the anesthesiologist was not certain of the study drug dose. The decision to exclude these patients was made before the postoperative period and thus no data were obtained.

Table 1. Demographic and Surgical Characteristics of Patients

Variable	Placebo	Nicotine
Age (yr)	46 ± 2	43 ± 3
Weight (kg)	67 ± 4	65 ± 5
Duration of Surgery (min)	147 ± 19	124 ± 9
Intraoperative fentanyl dose (μg/min)	2.3 ± 0.5	2.1 ± 0.2

There was no difference in age, weight, duration of surgery, or dose of narcotic used during surgery between groups. Values are mean ± SD.

Statistical Analysis

In previous studies using analog pain scores the SD was approximately 2 numerical analog pain units.[13] We calculated that to detect a difference of 2 numerical analog pain units with $\alpha = 0.05$ and 80% power, we would need to enroll 17 patients per group (StatMate; GraphPad software, San Diego, CA). Ten patients were enrolled per group as a pilot study requested by our Institutional Review Board. The difference between groups in pain score, morphine utilization, and hemodynamic variables were compared with one-way analysis of variance. The change in pain scores over time was determined with a one-way analysis of variance for repeated measures, where time was considered a continuous variable (Analyze-it for Microsoft Excel; Analyze-it Software, ltd., Leeds, England). All values are reported as mean (SD).

Results

The patients did not differ in age, weight, or duration of surgery. Of note, there was no difference in intraoperative fentanyl utilization between groups (table 1).

Patients in the placebo group had considerable postoperative pain. Despite treatment with morphine, the peak pain score in the placebo group was 7.6 (1.5) units and occurred 25 min after extubation of the trachea (zero time point, fig. 1a). Thereafter, pain scores in the placebo group were significantly reduced to a minimum of 6.4 (1.4) at 55 min after emergence ($P < 0.01$). The mean dose of patient-controlled analgesia morphine used by the control group was 12 (6) mg in the first hour (fig. 1b).

In contrast, patients who were treated with nicotine nasal spray just before emergence form the isoflurane anesthetic reported lower pain scores at all times during the first hour than patients who received placebo (fig. 1a; $P < 0.001$). The peak pain score in the nicotine group was 5.3 (1.6) units and occurred 35 min after surgery. Both groups reported increasing pain scores in the first 20 min after emergence when the effect of the fentanyl administered intraoperatively would be expected to be dissipating. Twenty-four hours after emergence from the general anesthetic, the patients in the nicotine group still reported lower pain scores than did

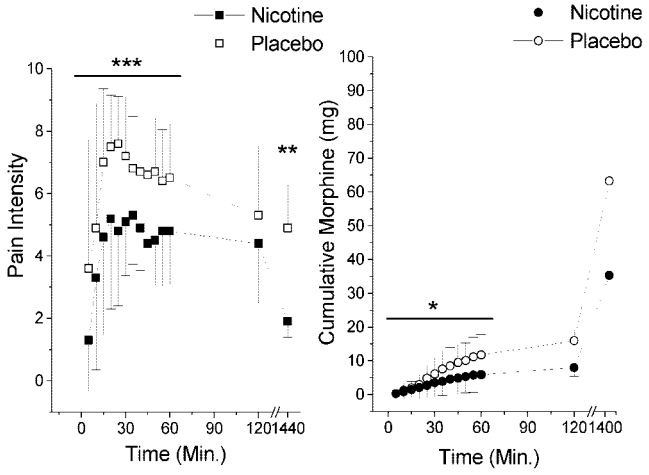

Fig. 1. Mean (± SD) numerical analog pain score and morphine utilization in the first hour after surgery. Zero time is extubation. (*A*) Patients treated with nicotine reported lower pain scores than those who received placebo during the first hour ($P < 0.001$). At 24 h pain was still reported to be less in the nicotine group ($P < 0.01$). (*B*) Cumulative morphine utilization. Patients who were treated with placebo used twice as much morphine in the first hour as those who were given nicotine nasal spray ($P < 0.05$). There was no difference in morphine utilization at later time points.

those in the placebo group (4.9 [1.4] placebo, 1.5 [0.5] nicotine; $P < 0.01$). In conjunction with decreased pain experience in the nicotine group, cumulative morphine utilization was less in the nicotine group than in the placebo group during the first hour, with 12 (6) mg used by the control group compared with 6 (5) mg used by the nicotine group (fig. 1b; $P < 0.05$). During the first 24 h after surgery, the patients who received placebo used 63 ± 11 mg of morphine and the patients in the nicotine group used 41 ± 9 mg morphine. The difference in morphine utilization at 24 h did not reach statistical significance.

Because nicotine nasal spray can cause increases in blood pressure and heart rate when used by unanesthetized subjects,[14–18] we measured these hemodynamic variables over the first hour in both groups. Systolic blood pressure was actually lower in the nicotine group, possibly in association with their lower reported pain scores (fig. 2a; 117 [3] *versus* 122 [3]; $P < 0.001$). There was no difference in heart rate or diastolic blood pressure over the first postoperative hour (fig. 2b).

Discussion

In this randomized, double blind, placebo-controlled trial; nicotine nasal spray significantly improved analgesia and reduced morphine requirements in women after uterine surgery. In studies on volunteers, this nicotine dose resulted in a mean peak plasma nicotine concentration of 4.7 (3.2) ng/ml 10 min after administration.[14] As such, a single dose of nicotine given under general anesthesia provided considerable analgesic benefit. Furthermore, pain reports remained significantly less in the patients 24 h after they received nicotine, although the distribution half-life of nicotine is only 2–3 h.[14,19–21] The terminal half-life is longer, however, reflecting release from less vessel rich stores. The prolonged effect of a single dose of nicotine might be a result of the continued presence of low nicotine concentrations and potential synergy with morphine. Because all patients received morphine postoperatively, we do not know if the excellent analgesic properties of nicotine are attributable to an additive effect of nicotine or a result of synergy with morphine. Activation of nicotinic receptors increases

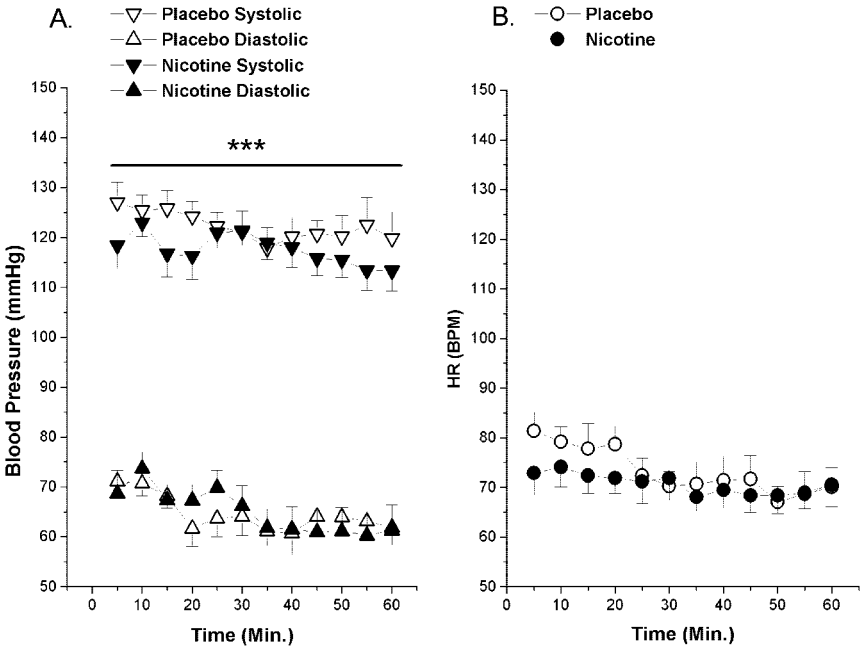

Fig. 2. Mean (± SD) hemodynamic variables in the first hour after surgery. (*A*) In the group treated with nicotine, the systolic blood pressure was lower than in the group treated with placebo ($P < 0.001$). There was no difference in diastolic blood pressure between groups. (*B*) There was no difference in heart rate between groups.

sensitivity to cocaine but it is not known whether there is a similar interaction with morphine.[22] Studies of analgesic synergy between the two agents can be undertaken in future studies in humans and other animals.

Alternatively, the analgesic effect at 24 h after surgery could be the result of a reduction in central or peripheral sensitization. A reduction in inflammation could also contribute to the analgesic action of nicotine. Recently, nicotinic agonists that activate $\alpha 7$ subunit containing nicotinic acetylcholine receptors on macrophages have been shown to have an antiinflammatory action.[23,24]

Nicotine has been approved for several years for over the counter use with transdermal administration, as a chewing gum, and as a nasal spray with a prescription. Its clinical safety profile has been found to be favorable.[25–29] However, nicotine has the potential to increase heart rate and blood pressure because it activates autonomic as well as central nicotinic receptors. Increased blood pressure has been put forward as a potential mechanism for the analgesic effects of nicotine.[9] In our study, however, we found no increase in blood pressure; in fact we found slightly lower systolic blood pressures in the patients treated with nicotine and no difference in diastolic blood pressure or heart rate. Signs of autonomic stimulation might be offset by the fact that the patients treated with nicotine had considerably less pain than did those treated with placebo. Also, isoflurane is a potent nicotinic antagonist and residual concentrations could blunt autonomic effects.[30] In a meta-analysis that included 3752 patients participating in randomized trials of nicotine replacement therapy, there was no difference in the incidence of adverse cardiovascular outcomes (myocardial infarction, stroke, tachycardia, arrhythmia, and angina) in patients randomized to receive nicotine.[31] However, the patients studied in the meta-analysis were all previous or current smokers. These patients might have been tolerant to the hemodynamic effects of nicotine.

In safety studies with the available modalities for nicotine administration, only mild nonhemodynamic side effects in smokers or nonsmokers were noted, including feelings of slight lightheadedness or dizziness.[14] In some settings, acute nicotine exposure can cause nausea.[31] Our study was not designed to detect changes in nausea, and we gave dolasetron prophylactically to all patients because of the high incidence of nausea after inhalation anesthesia for gynecological surgery.[32]

There are some obvious limitations of the current study that should be addressed in future work. The ideal dose and administration paradigm for nicotinic analgesia in the postoperative period needs to be developed. As all of our patients were women, we do not know if this treatment will be equally effective in men. Studies in animals and one study in humans suggest that nicotine is effective in a broader range of experimental pain paradigms in males than in females.[9,10,33] We do not know what type of nicotinic receptor mediates the analgesic action in our postoperative patients. Nicotinic receptors composed of $\alpha 4\beta 2$ and $\alpha 7$ subunits have been implicated in antinociceptive effects in animals.[34,35] Subtype selective nicotinic agonists might, in fact, produce superior therapeutic results.

Nicotine nasal spray had adjuvant analgesic activity after surgery in our study. The use of nicotine has the potential to spare opioid requirements and its use was apparently without side effects in our sample of healthy young, nonsmoking women. However, our study is small and was not designed to detect cardiovascular events that would be expected to have a low incidence in this population. In conclusion, we have demonstrated that nicotine nasal spray may be useful as an analgesic adjuvant in women after pelvic surgery. Until the side effect profile can be further addressed in larger studies, these findings should be considered preliminary.

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