Nicotine lozenges to promote brief preoperative abstinence from smoking: pilot study

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Abstract

**Background** Even brief preoperative abstinence from smoking can favorably affect intra-operative physiologic parameters such as carboxyhemoglobin concentrations, but many patients continue to smoke the morning of surgery.

**Objective** The goal of this pilot study was to determine the feasibility and potential effect size of nicotine lozenges as an adjunct to maintain brief preoperative abstinence, defined as not smoking the day of surgery.

**Methods** Forty six cigarette smokers scheduled for elective surgery were randomized in a double-blinded fashion to receive active or placebo nicotine lozenges, beginning the night prior to surgery, combined with brief advice to both groups to maintain abstinence on the morning of surgery. The primary outcome was the exhaled carbon monoxide (CO) level in the preoperative holding area.

**Results** Preoperative CO levels tended to be less in the active group (8.3 ± 7.5 and 12.7 ± 10.9 ppm in active and placebo groups, respectively, p = 0.12, Cohen's d = 0.47). Of the 46 subjects, 26 (57 %) tried at least one lozenge, with proportions similar in both groups. When those who tried at least one lozenge were analyzed, preoperative CO levels were significantly lower in those who received active lozenges (3.8 ± 3.0 and 12.7 ± 11.5 ppm in active and placebo groups, respectively, p = 0.009).

**Conclusion** This study suggests the feasibility of nicotine lozenges as an aid to maintain brief preoperative abstinence and provided preliminary evidence of efficacy. Methods to increase lozenge utilization, and a larger efficacy trial, are indicated.

Introduction

Cigarette smoking is a risk factor for several perioperative complications (1). Abstinence from smoking can reduce risk for some of these complications by allowing the effects of smoke constituents such as carbon monoxide to dissipate preoperatively (2-4). The minimum duration of abstinence needed for benefit is unknown (5;6), and may vary according to complication, but there are biologically-plausible reasons to believe that for some complications, even brief preoperative abstinence may be beneficial (7). However, despite efforts to encourage prolonged preoperative abstinence, current evidence suggests that in the absence of interventions the majority of smokers continue cigarette consumption until immediately before entering the surgical facility (8). Surgical providers insist upon fasting from food beginning the night before surgery to promote patient safety; a similar requirement to “fast” from cigarettes has been advocated (9). We have recently shown that physician advice to maintain brief preoperative abstinence is efficacious, but many smokers still are successful in doing so (10).

Nicotine replacement therapy (NRT) is a useful adjunct to help patients maintain prolonged abstinence; whether it might also be efficacious in helping smokers maintain brief preoperative abstinence is not known. The goal of this pilot study was to determine the feasibility and potential effect size of nicotine lozenges as an adjunct to maintain brief preoperative abstinence, defined as not smoking the day of surgery. The primary outcome of this randomized, double-blinded study in patients scheduled for elective surgical procedures was the exhaled CO concentration measured immediately prior to surgery, with a secondary outcome being the self-reported duration of smoking abstinence before admission to the surgical facility.

**Methods**

This study was approved by the Mayo Clinic Institutional Review Board.
Subjects were recruited from patients evaluated at the Mayo Clinic Rochester PreOperative Evaluation Center in preparation for elective surgery. Approximately 20% of adult patients undergoing a wide variety of surgical procedures at Mayo Clinic Rochester are seen in the POE (other surgical patients are evaluated preoperatively using other mechanisms). Eligibility criteria included age ≥ 18 years and current smoking before the scheduling of surgery, defined as > 100 cigarettes lifetime consumption and self-report of smoking either day or some days. Exclusion criteria included current receipt of pharmacotherapy and/or behavioral therapy for smoking cessation, or medical conditions such as pregnancy or unstable angina that would be relative contraindications to nicotine replacement therapy. Recruitment was performed on a convenience basis, and written informed consent was obtained.

After enrollment, subjects were randomized to receive either active or placebo nicotine lozenges. The time to first cigarette (< or ≥ 30 min) and the classification of surgical procedure (inpatient vs. outpatient) were designated as stratification factors (8), with the goal of randomizing equal numbers of subjects to each of the two interventions for each strata. Randomization was performed within these 4 strata. A randomization schedule for each strata was generated by our Biostatistics Core using blocks of size 4 to ensure that after every fourth subject enrolled in a given strata an equal number of subjects were assigned to each intervention group within that strata. Using these randomization schedules, study personnel that did not have any subject contact prepared study medication packets which were labelled according to subject ID numbers and contained the appropriate study medication for the treatment assignment for the given subject. At the time of enrollment, a subject was assigned the next sequential subject ID number for the appropriate strata and the appropriate study medication was dispensed.

All subjects regardless of group assignment received a brief (~ 2 min) behavioral intervention advising abstinence from smoking after 7 PM the night before surgery, including the potential benefits of abstinence, and asking them to consider using a lozenge at times when they would usually smoke, including the morning of surgery. After this intervention, the subjects received the study medication dosed according to time to first morning cigarette. If the subject normally smoked the first cigarette within 30 min of awakening, a 4 mg lozenge (or appropriately labeled placebo) was dispensed. If the subject normally smoked the first cigarette more than 30 min of awakening, a 2 mg lozenge (or appropriately labeled placebo) was dispensed. Each subject received 16 lozenges, sufficient to cover at least the period of time from 7 PM the night before surgery to the time of admission to the surgical facility (which could be up to 1-2 PM the following day).

Assessments were performed at the following times: 1) at the time of study enrollment (in the preoperative clinic); 2) on the morning of surgery, and 3) one week postoperatively. At the initial assessment, demographic information and co-morbidity were recorded, and a baseline smoking history was obtained (including the Fagerström Test for Nicotine Dependence (11) and the Minnesota Nicotine Withdrawal Questionnaire (12)). On the morning of surgery, self-reported smoking behavior since the last assessment was determined, with recent smoking assessed using expired carbon monoxide measurements. At one week after surgery, smoking behavior was assessed (via telephone).

Data analysis
The primary outcome for evaluating the effect of the study medication was the expired CO concentration measured in the preoperative holding area. Secondary outcomes included self-reported abstinence the morning of surgery and time to last cigarette. Comparisons were made using a two-sample t-test for continuous variable and Fisher’s Exact test for categorical variables. Two-sided p-values ≤ 0.05 were considered statistically significant.

Results
Forty-six subjects were randomized with 24 receiving placebo lozenges and 22 receiving active lozenges. All randomized subjects received the assigned intervention and underwent surgery. There were no significant differences between groups in baseline characteristics, with the exception that those in the placebo group had made a significantly greater number of quit attempts (Table 1). At baseline assessment, the majority of subjects in both groups expressed an intent to maintain preoperative abstinence.

Preoperative CO levels tended to be lower in the active group (8.3 ± 7.5 and 12.7 ± 10.9 ppm in active and placebo groups, respectively, p = 0.12). CO values were consistent with self-reported abstinence the morning of surgery (73% and 54% in active and placebo groups, respectively, p = 0.23). The accuracy of self-report was further suggested by plotting CO levels in self-reported abstinence and smokers (Figure 1), with a threshold of 10 ppm suggesting abstinence. The time to last cigarette tended to be shorter in the active group (Table 2).
Of the 46 subjects, 26 (56.5%) tried at least one lozenge, with proportions similar in both groups (Table 2). Of these, 2 subjects in each group objected to the initial taste of the lozenge and did not finish their first one. The proportion of subjects who used any lozenges and felt that they were helpful was similar in both groups, and the proportion of subjects who correctly identified their group assignment was not significantly different. When CO values were plotted according to whether any lozenges were used (Figure 2), lower preoperative CO levels clustered among those who used lozenges. When those who tried at least one lozenge were analyzed, preoperative CO levels were significantly lower in those who received active lozenges (Table 2). Among those who did not use at least one lozenge, there was no significant difference in CO levels (14.5 ± 13.4 and 9.0 ± 8.4 ppm in active and placebo groups, respectively, p=0.87).

Self-reported abstinence at postoperative day 8 was similar between groups.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=24)</th>
<th>Active (n=22)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (M ± SD)</td>
<td>49.8 ± 12.8</td>
<td>54.7 ± 14.0</td>
<td>0.21*</td>
</tr>
<tr>
<td>Sex (Male, %)</td>
<td>12 (50%)</td>
<td>10 (45%)</td>
<td>0.78**</td>
</tr>
<tr>
<td>Inpatient surgery (Y, %)</td>
<td>13 (55%)</td>
<td>12 (54%)</td>
<td>0.85**</td>
</tr>
<tr>
<td>Number of cigarettes per day (M ± SD)</td>
<td>17.9 ± 7.2</td>
<td>16.8 ± 6.7</td>
<td>0.61*</td>
</tr>
<tr>
<td>Previous quit attempts (M ± SD)</td>
<td>1.7 ± 0.7</td>
<td>1.0 ± 1.0</td>
<td>0.01*</td>
</tr>
<tr>
<td>FTND (M ± SD)</td>
<td>6.1 ± 1.4</td>
<td>6.7 ± 1.2</td>
<td>0.11*</td>
</tr>
<tr>
<td>Nicotine Withdrawal Score (M ± SD)</td>
<td>1.5 ± 1.0</td>
<td>1.5 ± 0.9</td>
<td>0.83*</td>
</tr>
<tr>
<td>Intent to abstain prior to surgery (Y, %)</td>
<td>19 (79%)</td>
<td>18 (82%)</td>
<td>1.0**</td>
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</table>

* Unpaired t test; **Fisher’s exact test

Table 2 Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=24)</th>
<th>Active (n=22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative CO (ppm, M ± SD)</td>
<td>12.7 ± 10.9</td>
<td>8.3 ± 7.5</td>
<td>0.12*</td>
</tr>
<tr>
<td>Self-reported morning abstinence (Y, %)</td>
<td>13 (54%)</td>
<td>16 (73%)</td>
<td>0.23**</td>
</tr>
<tr>
<td>Time to last cigarette (h, M ± SD)</td>
<td>16.7 ± 11.3</td>
<td>21.8 ± 19.5</td>
<td>0.29*</td>
</tr>
<tr>
<td>Preoperative Nicotine Withdrawal Score (M ± SD)</td>
<td>1.4 ± 0.9</td>
<td>1.3 ± 1.0</td>
<td>0.93*</td>
</tr>
<tr>
<td>Trying at least one lozenge (Y, %)†</td>
<td>16 (67%)</td>
<td>10 (45%)</td>
<td>0.23**</td>
</tr>
</tbody>
</table>

If yes:

- Do you think the lozenge contained nicotine? (Y, %) | 9 (53%) | 9 (75%) | 0.27** |
- Were lozenges helpful? (Y, %) | 7 (44%) | 5 (50%) | 1.0** |
- Preoperative CO levels (M ± SD) | 12.7 ± 11.5 | 3.8 ± 3.0 | 0.009* |
| Self-reported abstinence postoperative day 8 (Y, %) | 11 (46%) | 11 (50%) | 1.0** |

* Unpaired t test; **Fisher’s exact test; † of these, 2 subjects in each group objected to the initial taste of the lozenge and did not finish their first lozenge.

Discussion

The main findings of this pilot study are that the use of nicotine lozenges to aid preoperative abstinence is feasible and that there is preliminary evidence of efficacy for this indication.

Prolonged abstinence from smoking decreases the rate of perioperative complications (3), and tobacco interventions should be provided to presurgical patients as early as possible (2;13). However, these interventions are not always successful, nor are they feasible in many surgical settings. There are physiological reasons why even brief preoperative abstinence may have benefits (7). For example, increased CO levels are correlated with ischemia in anesthetized patients as CO decreases the oxygen-carrying capacity of the blood (14). Also, impaired tissue

Figure 1 Carbon monoxide (CO) levels in the preoperative holding area according to self-reported abstinence the morning of surgery.

Figure 2 Carbon monoxide (CO) levels in the preoperative holding area according to whether subjects reported using any lozenges.
tive method compared with nicotine gum and relatively ease of use compared with nicotine gum and relatively rapid onset of action and limited duration of effect compared with nicotine patches (16).

On an intention to treat basis, this pilot study found preliminary evidence of efficacy for the effect size of group assignment on preoperative CO levels, indicating a medium effect size. A somewhat smaller effect size was found for the secondary endpoint of self-reported time to first cigarette. These results were consistent with self-reported morning smoking status, which was highly accurate according to CO verification. For those subjects who tried lozenges, about half (in both groups) thought the lozenges were helpful, although patients were often unable to correctly identify lozenge content, perhaps suggesting some degree of placebo effect. Nonetheless, when analysis was restricted to those who actually used the lozenges, there was a significant treatment effect, even with relatively small numbers in each group. These findings suggest that there is preliminary evidence of efficacy.

These results also show that there are issues that would need to be addressed in a larger study or in implementation into clinical practice. Almost half of patients were not willing to try a lozenge to maintain abstinence, even in this study situation. Unused medications cannot be efficacious, and strategies should be explored to increase the lozenge utilization rate. Also, 15% of those who tried lozenges complained of a bitter taste and did not finish even a single lozenge (including two who received placebo lozenges), so that methods to increase the acceptability of NRT in this setting should also be investigated. This could include better instructions regarding this potential effect, or the use of nicotine gum or other delivery methods.

Conclusion

In conclusion, although this is a pilot study and was not powered to detect significant differences, this study suggests the feasibility of nicotine lozenges as an aid to maintain brief preoperative abstinence and provided preliminary evidence of efficacy. Given the potential benefits of preoperative abstinence, these results provide the rationale for a larger efficacy study.

Contribution details

Conception and design: DOW
Acquisition of data: DOW
Analysis and interpretation of data: DOW, SK
Drafting the article: DOW, SK
Revising the article critically for important intellectual content: DOW, SK
Final approval of the version to be published: DOW, SK

Competing Interests: None declared.

References