Efficacy of Fresh Lime for Smoking Cessation

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Objective: To determine the efficacy of fresh lime as a smoking cessation aid compared with nicotine gum.
Material and Method: A randomized, controlled trial was conducted between March 2009 and September 2009. Only regular smokers aged 18 or older who were willing to quit were randomized to receive either fresh lime (n = 47) or nicotine gum (n = 53). Smokers were excluded if they were using other smoking cessation aids, allergic to citrus, or had dental problems. Exhaled carbon monoxide (CO)-confirmed continuous abstinence rate (CAR) during week 9-12 was measured as the primary outcomes. To grade the severity of craving, a 100-mm visual analogue scale (VAS) was used.
Results: There was no significant difference in CO-confirmed CAR between the fresh lime group and the nicotine gum group during weeks 9-12 (61.7% vs. 66.0%; p = 0.65), although 7-day point prevalence abstinence at week 4 of the fresh lime users was statistically significant lower than those using nicotine gum (38.3% vs. 58.5%; p = 0.04). Cravings did not differ significantly between the groups, although fresh lime users tend to report more cravings intensity.
Conclusion: Fresh lime can be used effectively as a smoking cessation aid, although not as good as nicotine gum in reducing cravings.

Keywords: Fresh lime, Smoking cessation, Nicotine gum, Cravings

Smoking is the major preventable cause of chronic medical conditions and contributor to death worldwide[1,2]. Significant efforts led by World Health Organization (WHO) and several countries have formulated clinical practice guidelines for medical personnel to help smokers quit, particularly in developing countries where smoking rates continue to rise[3], but these remain unsuccessful[4]. Currently several effective medications exist for smoking cessation but steep costs prohibit widespread use, especially in poorer countries. Herbal remedies are cheaper and of particular interest is the fresh lime (*Citrus aurantifolia*), a common citrus native to Southeast Asia. To date there are no prospective, randomized trials using lime solely for smoking cessation. Our study was designed to determine the efficacy and safety of fresh lime alone for smoking cessation compared to nicotine gum.

Material and Method

The authors enrolled 100 of 110 eligible patients from March-September 2009 at the Panyananthaphikkhu Chonprathan Medical Center, Pakred, Nondhaburi, Thailand. Subjects were included if they were older than 18 years old, smoked regularly at least one year prior to study, desired to quit smoking, and signed informed consent. Enrollment was limited to only one smoker per household. Exclusion criteria included current dental problems, active peptic ulcer disease, psychiatric disorders, citrus allergy, pregnancy, use of illicit drugs, participation in another clinical trial and/or using any first-line smoking cessation aids within 30 days. The study protocol was approved by the Institutional Review Board of the Srinakharinwirot University. Conductance was in compliance with the Declaration of Helsinki ethical principles for medical

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research involving human subjects[5] and national regulations. Signed informed consents were obtained from all subjects.

Study design

This prospective two-arm randomized trial involved a 12-week treatment period with an additional single 24th week follow-up of the smoking status of all participants. Upon entry, a detailed smoking history and socio-demographic data was recorded by the smoking clinic nurse (SCN). All subjects were randomly allocated by block randomization technique[6] to receive either fresh lime or nicotine gum. Baseline exhaled carbon monoxide concentration measurement (CO) and the standard Fagerstrom Test for Nicotine Dependence (FTND)[7] was tabulated for each subject. Participants received a personalized message from the physician to stop smoking on the first day of treatment. Individual counseling lasting ~15-20 minutes, written instructions and self-report card for the use of gum or fresh lime were given to all participants by the SCN. All were instructed to record the severity of their cravings upon awakening by using 100-mm visual analogue scale (100-VAS) everyday[8].

Those assigned to fresh lime were instructed to use it whenever they craved cigarettes. To correctly use it, fresh lime needed to be washed and cut into 16 small pieces. Subjects were told to suck each piece of lime and thereafter chew the lime skin. To maintain freshness, the remaining slices were to be covered with plastic wrap and stored in the refrigerator. Total slices used per day were recorded in the self-report card.

The dosage of nicotine gum used in this group was based on FTND scores. Those with FTND score of 4 or above were given 4-mg nicotine gum. Lesser score subjects got 2-mg gum. They were advised to use the gum by "chew and park" technique whenever they craved a cigarette but not to exceed 20 pieces per day. Total number pieces of gum used per day were recorded in the self-report card.

The SCN phoned every 2-3 days during the initial month of study to remind them of technique and record keeping for both groups.

Follow-up protocol

Subjects returned for follow-up visits at 2, 4, 8, 12 and 24 weeks after their initial clinic visit. Upon each visit, the SCN performed CO, subjects were reinstructed on the proper use of nicotine gum or lime and given 10-minute individual counseling and self-report cards were collected. All participants received group behavioral therapy once in either week 2 or 4 of the 12-week treatment period. For those who did not show up to the clinic as scheduled, a phone call was made and a home visit would be made within the same week by the SCN for counseling and exhaled CO measurements.

Outcome measures

Continuous abstinence rate (CAR) from week 9-12 was the primary efficacy variable of the present study using CO confirmation. CAR from week 9-24 was a secondary efficacy variable. CAR from week 9 through a given point of time was defined as proportion of participants who self-reported having refrained from smoking any tobacco products and confirmed by CO of 10 ppm or less. Point prevalence abstinence rate (PAR) was also evaluated at week 4, 8, 12 and 24. PAR was defined as percentage able to abstain from smoking during the preceding week. Those who resumed smoking, used any other smoking cessation aids during the present study period, had CO > 10 ppm, or were non-adherent to treatment were considered to be unsuccessful abstinence.

Adverse events related to the use of fresh lime and nicotine gum experienced at least once were recorded and compared. Intensity of cravings after morning awakening in both groups were recorded on the day of clinic visits at week 2, 4, 8, 12 and 24 of the study using 100-mm VAS and compared.

Determination of sample size

The sample size was determined based on an earlier study[9] with a quit rate of 48.7% using nicotine gum vs. 21.8% using placebo[10]. To have a power of 80% (alpha = 0.05 by two-sided test) to detect treatment difference between nicotine gum and fresh lime, the estimated sample size was 46 per group, assuming the treatment difference was similar to the previous report.

Statistical analysis

Statistical analysis was performed using SPSS for windows (version 11.5, SPSS Incorporated). Normality of continuous data was checked by the Kolmogorov-Smirnov test. The parametric test was used to assess statistical significance occuring in normal distribution, otherwise nonparametric testing was used. Comparison of demographic and other baseline characteristics between the groups were made by Chi-square or Fisher's Exact test for categorical variables and using either student t-test or Mann-Whitney U test for continuous variables. CAR and

PAR for each given time point of both groups were determined and compared by using Chi-square test. Differences in adverse effects and cravings between groups were estimated by using Chi-square or Fisher's Exact test. To adjust time-change and other covariates, Cox regression analysis was performed. A p-value of less than 0.05 was considered statistically significant.

Results

Participant characteristics

Of 118 smokers screened, 8 were excluded because they did not meet the inclusion criteria, whereas 10 refused participation. The remaining 100 participants comprised the total enrollment and randomized to receive either fresh lime (n = 47) or nicotine gum (n = 53). Six participants from each group missed a routine follow-up clinic appointment and home visits were made by our SCN and substituted for these delinquencies.

Baseline demographics of the participants are shown in Table 1. No significant difference was noted between the groups in nicotine dependence levels (FTND score), age at starting smoking, and previous attempts to quit smoking. Those who received fresh lime appeared to be older and therefore had longer duration of smoking than the nicotine gum group. Those in the nicotine gum group had higher number of cigarettes smoked per day.

Efficacy

The primary end points of the study are reported in Table 2. The CAR for week 9-12 appeared to be higher in the group receiving nicotine gum, however, the difference did not reach statistical significance (61.7% vs.66.0%; p = 0.65) nor for week 9-24 (p = 0.61). For week 9-24, 55.3% of those in the fresh lime group were able to refrain from smoking continuously compared with 60.4% in the nicotine gum group.

Table 1. Baseline characteristics of the participants

Characteristic	Study Group		p-value
	Fresh Lime (n = 47)	Nicotine Gum (n = 53)	
Gender			
- Male	41 (87.2%)	49 (92.5%)	0.51 [a]
- Female	6 (12.8%)	4 (7.5%)	
Age (year)	47.23 ± 17.93	39.75 ± 13.37	0.02 [b]
	(median = 50.5)	(median = 38.0)	
Underlying diseases			
- COPD	3 (6.4%)	0 (0%)	1.00 [a]
- Asthma	1 (2.1%)	2 (3.8%)	1.00 [a]
- Hypertension	9 (19.1%)	9 (17.0%)	0.78 [d]
- Diabetes mellitus	3 (6.4%)	1 (1.9%)	0.34 [a]
Maximal number of cigarettes smoked per day	12.40 ± 6.22	17.79 ± 9.10	0.002 [c]
	(median = 10)	(median = 20)	
Type of tobacco products			
- Factory -made cigarette	36 (76.6%)	46 (86.8%)	0.37 [a]
- Roll-your-own cigarette	8 (17.0%)	6 (11.3%)	
- Both	3 (6.4%)	1 (1.9%)	
Duration of smoking (year)	30.83 ± 18.24	23.04 ± 12.0	0.01 [b]
	(median = 36.00)	(median = 21.00)	
Age at starting smoking	17.04 ± 4.74	17.30 ± 4.07	0.61 [c]
FTND score at entry	5.13 ± 2.28	5.74 ± 2.10	0.50 [b]
Alcohol drinking	23 (48.9%)	33 (62.3%)	0.18 [d]
Previous quit attempts			
- Never	12 (25.5%)	9 (17%)	0.30 [d]
- Yes	35 (74.5%)	44 (83.0%)	

[a]Fisher's Exact test, [b] t-test, [c]Mann-Whitney U test, [d]Chi-square

The 7-day point prevalence abstinence at each point of time appeared to be higher than the CAR (Fig. 1). At week 4, those who received fresh lime had a statistically significant lower abstinence rate than those in the nicotine gum group (38.3% vs. 58.5%; p = 0.04). By the 8th week 63.8% vs. 66.0% (p = 0.82) fresh lime-nictotine gum respectively were able to quit successfully and by week 12 was 72.3% vs. 75.5% (p = 0.72). In the final week of treatment, no statistically significant difference was noted in the abstinence rate between groups (68.1% vs. 71.7%; p = 0.69).

Univariate analysis showed that age, number of daily cigarette smoked and duration of smoking of both groups were not equivalent. Cox regression analysis was, therefore, utilized to avoid their confounding effects on the efficacy assessment which still showed no difference of abstinence rates between the groups throughout 24-week follow-up (Hazardous ratio = 0.72; 95% CI = 0.43-1.19) (Fig. 2).

Adverse events and cravings

In the nicotine gum group, sore mouth (47.1%) and dyspepsia (41.5%) were the most common side effects during the treatment. No serious adverse event was reported at any time for either group participants. Withdrawal symptoms among the fresh lime participants were similar to those who received nicotine gum. The intensity of cravings recorded at each clinic visit by 100-VAS was higher in the fresh lime group than nicotine gum participants at week 2, 4 and 8 but identical by week 12 and 24 (Fig. 3). Regardless of the type of treatment, cravings appeared to diminish substantially over time.

Discussion

According to the present study, by the end of the third study month, the CAR of smokers who received fresh lime treatment was 61.7%, compared with 66.0% among those who were given nicotine gum. There could have not been a placebo effect of lime since other studies have shown only a 10-20% success rate with placebo[11-13]. The authors abstinence rates are, in fact, in accordance with previous studies in Asian populations that used nicotine replacement therapy
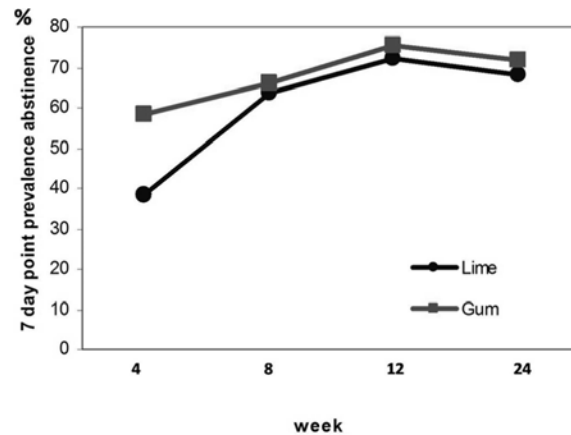

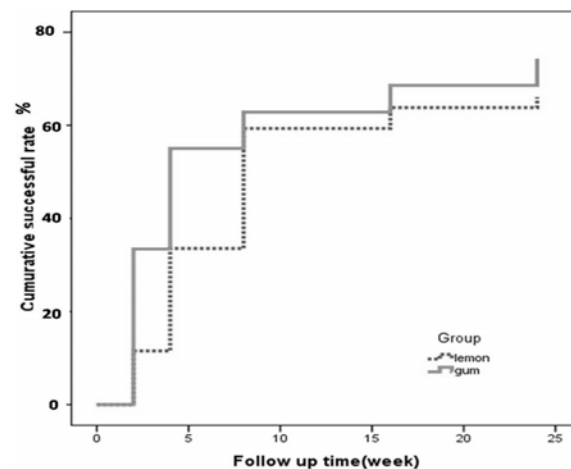**Fig. 1** Seven-day point prevalence abstinence verified by exhaled CO concentrations

Fig. 2 Successful abstinence rate of fresh lime group and nicotine gum group after adjusting for age, duration of smoking and number of cigarette smoked per day by using Cox regression analysis throughout 24-week follow-up

Table 2. Exhaled CO-verified continuous abstinence rates at clinic visits

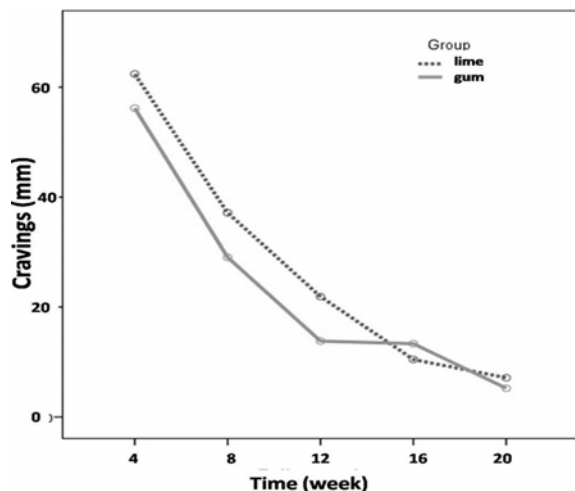| Weeks	Study Groups		p-value
	Fresh Lime (n = 47)	Nicotine Gum (n = 53)	
9-12	29 (61.7%)	35 (66.0%)	0.65[a]
9-24	26 (55.3%)	32 (60.4%)	0.61[a]

[a] Chi square test

Fig. 3   Cravings on 100-mm VAS score

(NRT) as smoking cessation aids[10-12,14]. All of those trials demonstrated superiority of NRT over placebo with abstinence rates ranging between 50% and 60% at 3 months, similar to our findings for either nicotine or fresh lime.

Those who received fresh lime appeared to have higher 100-VAS scores than those in the nicotine gum group at week 2, 4 and 8. However the intensity of cravings between groups eventually became identical at week 12 and 24. This interesting finding may indicate that fresh lime, although not as good as nicotine gum in reducing cravings initially, it is still effective when used in combination with good counseling and careful monitoring.

The precise mechanisms whereby fresh lime helps in smoking cessation remain poorly understood. It could be associated with combating the known declination of the serum levels of ascorbic acid caused by smoking[15,16]. On an interesting note, one study reported that inhaled vitamin C supplement may be helpful for smokers who wish to quit[17]. While vitamin C could be one of the mechanisms of action of lime in smoking abstinence, the role of several other active substances found in lime, such as citric acid, malic acid, etc., remains inconclusive.

One striking difference between our groups was the incidence of adverse effects. Only one participant developed tooth sensitivity in the fresh lime group while 41-47% of the nicotine gum users reported sore mouth and/or dyspepsia which required pharmacologic intervention. Similarly, the incidence of adverse effects in other trials using nicotine gum are in the range of 30-50% [11,14].

Some limitations of the present study should be noted. First is the small sample size. The sample size determination was based on prior study comparing the efficacy of nicotine gum vs. placebo. However, it seems clear from our results that fresh lime is, in fact, not a placebo and has real efficacy for smoking cessation. Despite this, our results may shed light on smoking cessation with this natural agent that is much cheaper and more readily accessible to smokers than nicotine replacement therapy, particularly those living in poor and developing countries. Further study with larger numbers of participants is, therefore, necessary. Another limitation was in the present study design that did not assure matched-pairs. This led to some characteristics, in particular the number of cigarette smoked per day and the duration of smoking not being identical between the two groups. Although such difference could affect the outcomes, the authors believe that the longer duration of smoking yet less number of cigarettes smoked per day among fresh lime participants would had cancelling effects on one another. Arguably, the results remained unchanged after the different age, number of daily cigarettes smoked and duration of smoking were adjusted by Cox regression analysis (Fig. 3).

In conclusion, fresh lime alone can be used as an effective smoking cessation aid. It should be considered as an alternative smoking cessation aid, especially among those who cannot afford first-line medications.

References

1. Shafey O, Eriksen M, Ross H, Mackay J. Deaths. In: Shafey O, Eriksen M, Ross H, Mackay J, editors. The tobacco atlas. 3rd ed. New York: McGraw-Hill;

2009: 38-9.

2. Kenfield SA, Wei EK, Rosner BA, Glynn RJ, Stampfer MJ, Colditz GA. Burden of smoking on cause-specific mortality: application to the Nurses' Health Study. Tob Control 2010; 19: 248-54.

3. Abdullah AS, Husten CG. Promotion of smoking cessation in developing countries: a framework for urgent public health interventions. Thorax 2004; 59: 623-30.

4. Bauld L, Boyd KA, Briggs AH, Chesterman J, Ferguson J, Judge K, et al. One-year outcomes and a cost-effectiveness analysis for smokers accessing group-based and pharmacy-led cessation services. Nicotine Tob Res 2011; 13: 135-45.

5. World Medical Association. WMA Declaration of Helsinki ethical principles for medical research involving human subjects [Internet]. 2010 [cited 2010 Dec 22]. Available from: http://www.wma.net/en/30publications/10policies/b3/

6. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976; 34: 585-612.

7. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991; 86: 1119-27.

8. Guthrie SK, Ni L, Zubieta JK, Teter CJ, Domino EF. Changes in craving for a cigarette and arterial nicotine plasma concentrations in abstinent smokers. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 617-23.

9. Chan YH. Randomised controlled trials (RCTs)—sample size: the magic number? Singapore Med J 2003; 44: 172-4.

10. Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerstrom KO. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. Chest 1995; 108: 447-51.

11. Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med 2002; 162: 1267-76.

12. Jarvis MJ, Raw M, Russell MA, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. Br Med J (Clin Res Ed) 1982; 285: 537-40.

13. Vinnikov D, Brimkulov N, Burjubaeva A. A double-blind, randomised, placebo-controlled trial of cytisine for smokingcessation in medium-dependent workers. J Smok Cessat 2008; 3: 57-62.

14. Rungruanghiranya S, Ekpanyaskul C, Hattapornsawan Y, Tundulawessa Y. Effect of nicotine polyestex gum on smoking cessation and quality of life. J Med Assoc Thai 2008; 91: 1656-62.

15. Lykkesfeldt J, Prieme H, Loft S, Poulsen HE. Effect of smoking cessation on plasma ascorbic acid concentration. BMJ 1996; 313: 91.

16. Sorensen LT, Toft BG, Rygaard J, Ladelund S, Paddon M, James T, et al. Effect of smoking, smoking cessation, and nicotine patch on wound dimension, vitamin C, and systemic markers of collagen metabolism. Surgery 2010; 148: 982-90.

17. Levin ED, Behm F, Carnahan E, LeClair R, Shipley R, Rose JE. Clinical trials using ascorbic acid aerosol to aid smoking cessation. Drug Alcohol Depend 1993; 33: 211-23.

ประสิทธิภาพของมะนาวสดในการช่วยเลิกบุหรี่

สุทัศน์ รุ่งเรืองหิรัญญา, ฉัตรชัย เอกปัญญาสกุล, ชนินทร สกุลอิสริยาภรณ์, ประภาดา วัชรนาถ,
กัญญานิษฐ์ อัครกุลวัสส์

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของมะนาวสดในการช่วยเลิกบุหรี่เปรียบเทียบกับหมากฝรั่งนิโคตีน

วัสดุและวิธีการ: เป็นการศึกษาแบบสุ่มโดยใช้อาสาสมัครที่สูบบุหรี่เป็นประจำและมีอายุตั้งแต่ 18 ปีขึ้นไป
และประสงค์ที่จะเลิกบุหรี่ โดยแบ่งผู้ป่วยออกเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับมะนาวสด (จำนวน 47 ราย) ส่วนอีกกลุ่มหนึ่ง
ได้รับหมากฝรั่งนิโคตีน (จำนวน 53 ราย) ผู้ป่วยที่ใช้ยาเลิกบุหรี่ชนิดอื่น ๆ แพ้มะนาว หรือมีปัญหาสุขภาพฟัน
จะถูกคัดออกจากโครงการ อัตราการเลิกบุหรี่สำเร็จระหว่างสัปดาห์ที่ 9-12 จะต้องถูกยืนยันด้วยเครื่องตรวจวัดระดับ
ก๊าซคาร์บอนมอนอกไซด์ในลมหายใจ และใช้การวัดอาการอยากบุหรี่ด้วย 100-mm VAS

ผลการศึกษา: อัตราการเลิกบุหรี่สำเร็จของทั้งสองกลุ่มระหว่างสัปดาห์ที่ 9-12 นั้นไม่แตกต่างกันทางสถิติ (61.7%
vs. 66.0%; p = 0.65) แม้ว่า 7-day point prevalence abstinence ในสัปดาห์ที่ 4 นั้น กลุ่มที่ได้รับมะนาวจะต่ำกว่า
ของกลุ่มที่ได้รับหมากฝรั่งนิโคตีนอย่างมีนัยสำคัญทางสถิติ (38.3% vs. 58.5%; p = 0.04) ส่วนอาการอยากบุหรี่นั้น
ไม่แตกต่างกันในทั้งสองกลุ่ม แม้ว่ากลุ่มที่ได้รับมะนาวจะมีอาการอยากบุหรี่ที่รุนแรงกว่ากลุ่มที่ได้รับหมากฝรั่งนิโคตีน

สรุป: มะนาวสดมีประสิทธิภาพในการช่วยเลิกบุหรี่ แม้ว่าจะช่วยลดอาการอยากบุหรี่ได้ไม่ดีเท่ากับหมากฝรั่ง
นิโคตีนก็ตาม