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A Randomized Controlled Open Comparative Trial of Varenicline vs Nicotine Patch in Adult Smokers

– Efficacy, Safety and Withdrawal Symptoms (The VN-SEESAW Study) –

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Background: It has been suggested that anti-smoking therapy gives encouraging results, but this has not been verified by well-randomized study protocols. The present study was a randomized controlled trial of varenicline vs nicotine patch in adult smokers for comparison of efficacy, safety and withdrawal symptoms.

Methods and Results: The 32 adult smokers were randomly divided into a varenicline group (VG, n=16) and a nicotine patch group (NG, n=16). The primary endpoints were the 12- and 24-week smoking-abstinence rates, safety and withdrawal symptoms including stress. No significant difference in abstinence rates was observed between the 2 groups over weeks 9–12 (71.4% vs 78.6% in the VG and NG, respectively), and weeks 9–24 (64.3% vs 71.4%, respectively). The frequencies of inability to concentrate at 2, 4, and 8 weeks, and wakeful nights at 2 weeks were higher in the VG than in the NG. Adverse side-effects associated with a gastrointestinal disorder occurred in 14 cases and 1 case in the VG and NG, respectively, and skin allergy was seen in 0 and 9 cases, respectively.

Conclusions: The selection of treatment depends on the balance of desired acuteness of cessation of smoking and side-effects, such as psychiatric and gastrointestinal problems or skin allergy. (*Circ J* 2010; **74:** 771–778)

Key Words: Comparative trial; Nicotine patch; Smoking-abstinence rates; Varenicline; Withdrawal symptoms

Smoking has been identified as a preventable risk factor for disease in both developed and developing countries.[1] As reported by WHO,[2] if current smoking patterns continue, 1 billion people will die from tobacco-related causes in the 21st century, which is 10-fold more than the 100 million in the 20th century. In Japan, the incidence of smoking among males has decreased from 50.8% in 1998 to 39.4% in 2007, remaining stable among females at approximately 10–11%.[3] Compared with developed countries in the West, Japanese males are more likely to smoke, whereas females are less likely, and younger women, especially those in their 20 s and 30 s, are increasingly more likely to smoke.[3]

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The first anti-smoking program in Japan, the Kenko Nippon 21 project, was started in March 2000. In May 2003, the Health Promotion project started, and second-hand smoke was targeted. In August 2006, the Cancer Protection program started, and anti-smoking education was advanced. The government set a goal of 0% smoking among youths, and this goal has not yet been achieved. In addition, anti- and stop-smoking programs have been strengthened. As part of the Tobacco Control Project, smoking bans were started in March 2004, and ban on packaging was approved in July 2005. In April 2006, treatment for nicotine addiction was covered by medical insurance, and nicotine replacement therapy became available at many hospitals. TASPO, which is a type of ID card for obtaining cigarettes from vending machines, was introduced in 2008 to make it more difficult for young people to buy tobacco. Finally, in May 2008, varenicline became available for clinical use in Japan. Varenicline is a newly synthesized and orally administered small molecule that binds the $\alpha 4\beta 2$ nicotine acetylcholine receptor with partial agonistic action.[4–6]

In this study, we performed a head-to-head randomized controlled open comparative trial of varenicline vs nicotine patch in Japanese adult smokers. Prior evidence has revealed associations between smoking and stress, and that smoking reduces anxiety and stress.[7,8] Therefore, this VN-SEESAW Study examined efficacy, safety and withdrawal symptoms including stress.

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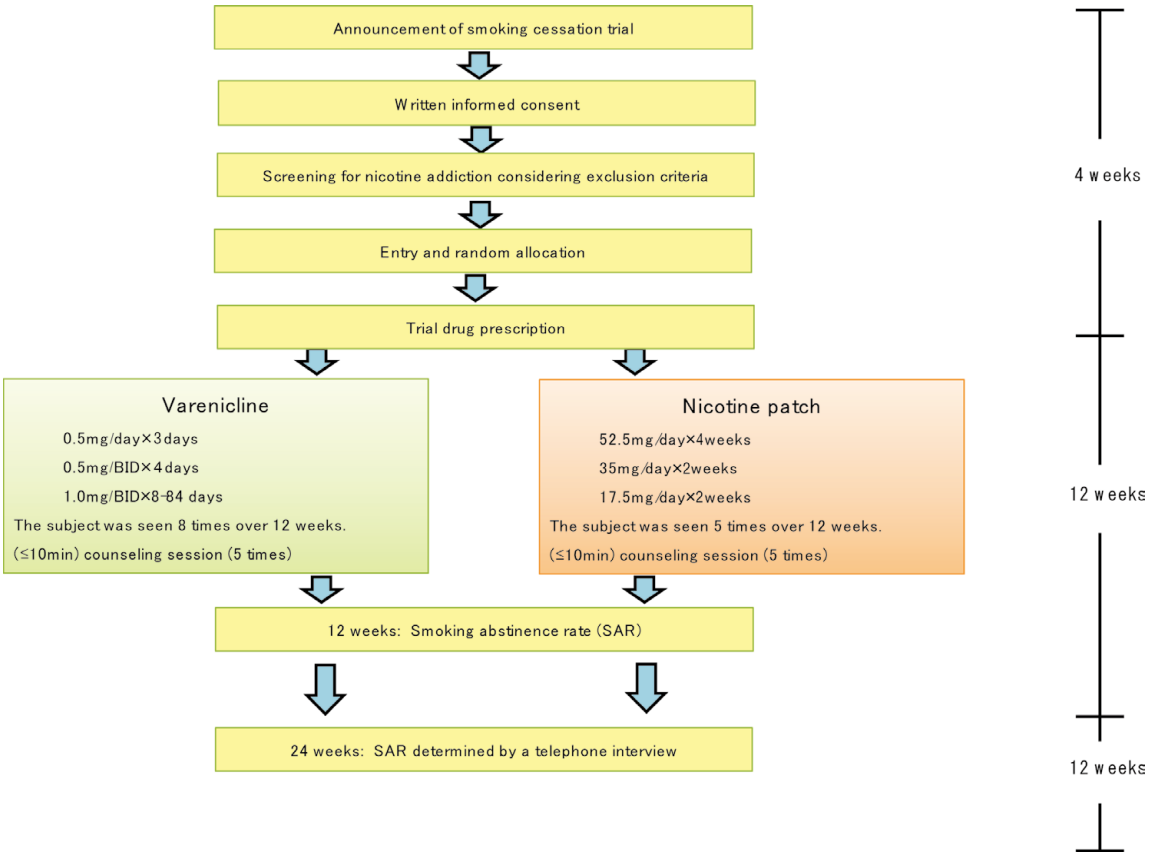

Figure 1. Outline of the study.

Methods

Study Design

This was a randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers, and the efficacy, safety and withdrawal symptoms were compared between the 2 groups. This study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from the Independent Review Board (IRB) of Fukuoka University Hospital [No. 7-05(08-27)]. All participants gave written informed consent prior to any procedures. The study started in August 2008 and ended in November 2009.

Study Population

At the beginning of the trial, Fukuoka University Extension Center contacted citizens of Fukuoka City (Nanakuma area) by advertising the research protocol, and the anti-smoking campaign and the details of this trial were described. In total, 32 Japanese adult smokers with nicotine addiction (Tobacco Dependence Screener (TDS) ≥5, and Brinkman index ≥200) aged between 27 and 64 years who all wished to stop smoking immediately were recruited and enrolled for treatment at the Smoking Cessation Clinic of Fukuoka University Hospital. Participants were excluded if they had a history of cancer, had attended a smoking cessation clinic within the previous 12 months, had diabetes mellitus requiring insulin injections, drug or alcohol dependence, or psychological disorders, or were pregnant or possibly could become pregnant. Other exclusion criteria were clinically allergic reactions to drugs or adhesive tape, skin disorders, hemodialysis, severe hypertension and spastic angina pectoris, severe heart failure, recent (<3 months) myocardial infarction or stroke. Subjects who were being co-administered cimetidine, fenacetin, caffeine etc were also excluded.

Interventions

The outline of the clinical study is shown in Figure 1. After the study was advertised to the people in the Nanakuma area (Fukuoka City) who wished to stop smoking immediately, screening for nicotine addiction was conducted while considering the exclusion criteria, and the 32 eligible participants were selected. They were randomized within 4 weeks by computer in a 1:1 ratio to either 12 weeks of varenicline (0.5–2 mg daily: 0.5 mg after meals for 3 days, 0.5 mg BID for days 4–7, 1 mg BID for days 8–84), or a transdermal nicotine patch for 8 weeks (52.5–17.5 mg nicotine daily: 52.5 mg for 4 weeks, 35 mg for 2 weeks, and 17.5 mg for 2 weeks), according to the manual of Japanese anti-smoking therapy.[9] Based on the smoking population of Japan (40% of males, 12% of females), randomization was conducted with a male:female ratio of 3:1. Each protocol consisted of 12 weeks of follow-up at the outpatient clinic with 5–8 visits, and smoking abstinence rates at 24 weeks were determined by telephone interview.

Table 1. Characteristics and Smoking History of the Participants

Characteristics	Varenicline (n=14)	Nicotine patch (n=14)	Z	P value
Age (years)	45.4±12.98	46.8±10.71	–0.299	0.765
Sex (%)				
Male	85.7	78.6		
Female	14.3	21.4		
Weight (kg)	67.29±9.03	66.20±13.30	–0.414	0.679
BMI	23.7±3.26	23.6±3.64	–0.459	0.646
Age smoking started (years)	18.1±2.70	18.9±1.98	–1.291	0.197
Duration of smoking (years)	25.4±11.53	27.1±10.8	–0.299	0.765
Cigarettes smoked per day	27.9±10.87	25.4±7.96	–0.801	0.423
Brinkman index	726.4±479.0	677.5±358.5	–0.023	0.982
TDS score	7.64±1.60	7.57±1.55	–0.141	0.888
Previous smoking abstinence experience (%)	71.4	71.4		
Previous use of nicotine patch (%)	7.1	7.1		
Previous use of nicotine gum (%)	21.4	0		

Data are mean±SD.
BMI, body mass index; Brinkman index, cigarettes per day×smoking history (years); TDS, Tobacco Dependence Screener.

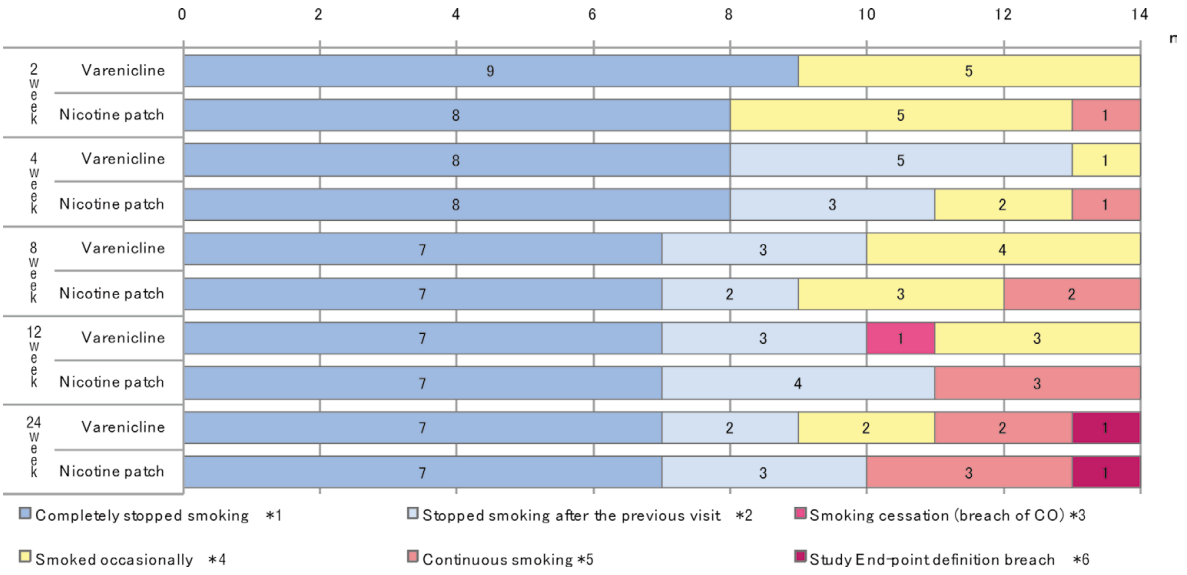

Figure 2. Relationship between the study schedule and smoking data in both groups. *1 (completely stopped smoking): subjects who had completely stopped smoking. *2 (stopped smoking after the previous visit): subjects who had stopped smoking at weeks 2, 4 and 8. *3 (smoking cessation, breach of CO): subjects who had self-reported no smoking, but had an end-expiratory CO concentration >8 ppm. *4 (smoked occasionally): subjects who smoked >1 cigarette after the previous visit. *5 (continuous smoking): subjects who showed continuous smoking. *6 (study endpoint definition breach): subjects who had self-reported stopped smoking in 24 weeks, but showed evidence of smoking in 9–12 weeks.

Study Endpoints: Efficacy, Safety and Withdrawal Symptoms

The primary endpoint of this trial was the incidence of smoking cessation in the 2 groups at weeks 9–12 and weeks 9–24, and the safety and withdrawal symptoms, including stress, at weeks 12. Reports of no smoking at weeks 12 were confirmed by measuring the end-expiratory CO concentration. If the end-expiratory CO concentration was >8 ppm, the subject was not considered to have achieved smoking abstinence. Withdrawal symptoms were assessed using the Minnesota Nicotine Withdrawal Scale (MNWS),[10] which contains 9 items, each of which is assigned a score from 1 (not at all) to 4 (extreme yes), and total scores were determined at weeks 2, 4, 8 and 12, as described previously.[10] A 15-item self-administered questionnaire was also used. Stress was evaluated using self-monitoring questionnaires, the Stress Check List (SCL: 30 items), and the State–Trait Anxiety Inventory (STAI: A-Trait and A-State), and adverse effects, including the results of laboratory examinations, were monitored.

Table 2. MNWS Scores From Week 2 to Week 12

MNWS	Group	Week 2	Week 4	Week 8	Week 12
Withdraw al symptoms total score	Varenicline	14.86±3.55	13.64±2.34	13.14±3.78	12.29±3.17
	Nicotine patch	12.50±2.74	13.00±3.19	12.36±2.9	12.21±2.33
Urge to smoke (craving)	Varenicline	1.79±0.80	1.50±0.65	1.43±0.51	1.29±0.47
	Nicotine patch	1.64±0.63	1.29±0.47	1.29±0.47	1.21±0.43
Depressed mood	Varenicline	1.21±0.43	1.21±0.43	1.07±0.27	1.07±0.27
	Nicotine patch	1.29±0.61	1.07±0.27	1.00±0.00	1.21±0.58
Irritability, frustration, or anger	Varenicline	1.50±0.52	1.36±0.50	1.21±0.58	1.29±0.61
	Nicotine patch	1.43±0.51	1.36±0.50	1.21±0.43	1.29±0.47
Feeling of uneasiness	Varenicline	1.21±0.43	1.29±0.47	1.21±0.58	1.21±0.43
	Nicotine patch	1.14±0.36	1.07±0.27	1.07±0.27	1.14±0.53
Inability to concentrate	Varenicline	1.29±0.47	1.36±0.50	1.43±0.51	1.29±0.47
	Nicotine patch	1.00±0.00 *	1.07±0.27 †	1.14±0.36 †	1.21±0.43
Lack of self-composure	Varenicline	1.43±0.65	1.21±0.43	1.36±0.63	1.29±0.47
	Nicotine patch	1.21±0.43	1.14±0.36	1.14±0.36	1.07±0.27
Increased appetite	Varenicline	2.50±1.02	2.21±1.19	2.21±0.97	2.14±0.95
	Nicotine patch	2.21±0.97	2.43±0.94	2.43±0.85	2.43±0.85
Difficulty going to sleep	Varenicline	1.77±1.01	1.50±0.85	1.36±0.84	1.21±0.43
	Nicotine patch	1.29±0.47	1.71±1.07	1.43±0.85	1.29±0.47
Wakeful nights	Varenicline	2.29±0.99	2.00±1.04	1.86±1.10	1.50±0.76
	Nicotine patch	1.29±0.47 **	1.86±1.03	1.64±0.93	1.36±0.50
No. of subjects (%)	Varenicline	14 (100.0)	14 (100.0)	13 (92.9)	12 (85.7)
	Nicotine patch	11 (78.6)	13 (92.6)	12 (85.7)	14 (100.0)
Total no. of appearances	Varenicline	59	57	39	37
	Nicotine patch	40	40	30	35

Data are mean ± SD. Mann-Whitney test: †P≤0.1, *P≤0.05, **P≤0.01.
MNWS, Minnesota Nicotine Withdrawal Scale.

Analysis

The 32 patients were divided evenly into varenicline (VG) and nicotine patch (NG) groups, and adverse effects were analyzed for all subjects. The 4 subjects who dropped out during follow-up (2 in VG, 2 in NG) were excluded from the analyses of efficacy and withdrawal symptoms, and thus the results from 28 patients (14 in each group) were used to analyze efficacy and withdrawal symptoms including stress. Statistical analysis was performed using SPSS software package (version 16.0 J, for Windows; Chicago, IL, USA) at Fukuoka University. Categorical variables were compared between groups by a chi-square analysis. The differences in continuous variables between groups were examined by the Mann-Whitney test or Wilcoxon's rank-sum test. Data are presented as the mean and standard deviation of the mean unless indicated otherwise. Differences were considered to be statistically significant when the P-value was 0.05 unless indicated otherwise.

Results

Table 1 shows the baseline characteristics of the 28 subjects, 14 each in the VG and NG. Age, sex, body weight, body mass index (BMI), age at which smoking started, number of years smoking, number of cigarettes/day, Brinkman index, TDS, prior smoking abstinence experiences, and previous use of nicotine patch or nicotine gum were all similar between the 2 groups.

Efficacy was assessed in terms of the smoking abstinence rates at weeks 9–12 and weeks 9–24. One patient in the VG showed an end-expiratory CO concentration >8 ppm at 12 weeks and was excluded from the analysis of smoking cessation. The smoking abstinence rates were 71.4% and 78.6% at weeks 9–12 and 64.3% vs 71.4% at weeks 9–24 in the VG and NG, respectively. Figure 2 shows the relationship between the study schedule (period) and smoking data in both groups (ie, the number of subjects who had completely stopped smoking, those who had stopped smoking after the previous visit, those who had self-reported no smoking but showed an end-expiratory CO concentration >8 ppm, those who smoked occasionally (smoked >1 cigarette after the previous visit), and those who showed continuous smoking). Overall, no significant difference was observed between the 2 groups. In the VG, 3 subjects started smoking 1–3 cigarettes at 9–12 weeks, although 2 showed an end-expiratory CO concentration <8 ppm, and 1 did not smoke at weeks 9–12 but had an end-expiratory CO concentration >8 ppm, so a total of 4 patients failed to stop smoking in this group. In the NG, 1 patient continued smoking 5–12 cigarettes/day, 1 smoked every day after 8 weeks, and 1 smoked 1–3 cigarettes/day at 9–12 weeks, so a total of 3 patients did not stop smoking.

Withdrawal symptoms were assessed using the MNWS as noted earlier. The total withdrawal symptom score (MNWS) in the VG was higher than that in the NG at 2 weeks (14.86±3.55 vs 12.50±2.74), but this difference was not statistically significant. However, in detail, the frequencies of an inability to concentrate at 2, 4, and 8 weeks (1.29±0.47 vs 1.00±0.00, 1.36±0.50 vs 1.07±0.27, 1.43±0.51 vs 1.14±0.36, P=0.034, 0.070, 0.100, respectively), wakeful nights at 2 weeks (2.29±0.99 vs 1.29±0.47, P=0.003), feeling uneasiness at 4 weeks (1.29±0.47 vs 1.07±0.27, P=0.146), and a lack of self-composure at 12 weeks (1.29±0.47 vs 1.07±0.27, P=0.146) were higher in the VG than in the NG (Table 2).

Table 3. Personal Feelings and Stress

		Varenicline (n=14)	Nicotine patch (n=14)	Z	P value
Items that reflect not smoking	Week 2	4.86±2.91	5.43±3.57	−0.209	0.835
	Week 4	5.29±3.25	6.21±3.62	−0.649	0.517
	Week 8	5.50±3.23	6.86±3.28	−0.880	0.379
	Week 12	5.79±3.75	7.50±3.67	−0.993	0.321
SCL	First visit	5.64±3.86	5.14±4.11	−0.487	0.626
	Week 2	3.57±2.10	3.07±2.53	−0.767	0.443
	Week 4	3.21±3.56	2.93±4.51	−0.633	0.527
	Week 8	2.57±2.82	2.07±2.09	−0.327	0.743
	Week 12	2.79±2.83	1.57±1.60	−1.062	0.288
STAI A-trait anxiety	First visit	42.21±9.12	41.21±6.03	−0.414	0.679
	Week 2	39.36±7.34	38.86±7.16	−0.345	0.730
	Week 4	36.57±8.07	38.64±5.23	−0.438	0.662
	Week 8	36.21±7.97	37.29±6.50	−0.276	0.782
	Week 12	36.64±7.90	38.08±7.24	−0.414	0.679
STAI A-state anxiety	First visit	37.79±7.06	37.71±7.42	−0.963	0.963
	Week 2	34.50±9.37	37.36±4.85	−0.160	0.160
	Week 4	34.00±9.64	34.57±6.91	−0.765	0.765
	Week 8	34.29±7.88	36.43±5.24	−0.345	0.345
	Week 12	33.50±8.70	35.50±6.48	−0.629	0.629

Data are mean±SD. Mann-Whitney test: †P≤0.1, *P≤0.05, **P≤0.01, ***P≤0.001.
SCL, Stress Check List; STAI, State-Trait Anxiety Inventory.

Table 4. Adverse Events During the Study Period

Trial drug	Subjective symptoms·Other findings (n=32)		Unusual laboratory examination (n=28)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Varenicline				
Cases seen (n)	14	13	5	5
Cases seen (%)	87.5	81.25	35.71	35.71
No. of appearances	43	29	11	7
No. of appearances per subject	3.00±1.41			
	P=0.028*	P=0.099†	NS P=0.916	NS P=0.538
Nicotine patch				
Cases seen (n)	13	11	6	4
Cases seen (%)	81.25	68.75	42.86	28.57
No. of appearances	23	16	6	4
No. of appearances per subject	1.77±0.93			

Data are mean±SD. Mann-Whitney test: †P≤0.1, *P≤0.05.

Personal Feelings and Stress

Self-Monitoring Questionnaires The results of the 15-item self-administered questionnaire were also obtained at 2, 4, 8 and 12 weeks in both groups: an increase in appetite was reported in 9 and 13 cases in the VG and NG, respectively, good gastrointestinal conditions were reported in 3 and 7 cases, and the ability to detect flower scents was noted in 4 and 11 cases, respectively, which shows that varenicline was associated with less of a positive olfactory response, while good respiration was reported in 10 and 5 cases, respectively. The items that reflected a realization of the effects of non-smoking were significantly increased in the NG during 12 weeks (5.43±3.57, 6.21±3.62, 6.86±3.28, and 7.50±3.67, at weeks 2, 4, 8, and 12, respectively, P≤0.05), but no changes were observed in the VG (Table 3).

Changes in Stress The SCL (30 items) was used, and in both groups the SCL scores tended to decrease during the trial (Table 3). None of the patients was in a deep state of stress, and moderate stress was observed in only 1 subject in each group at 0 and 4 weeks. The STAI A-Trait (specific for uneasiness) reflects a personal component of stress: ≥44 points in males and 45 points in females shows personal uneasiness, which was observed in 57.1% and 28.6% of the subjects in the VG and NG, respectively, and thus personal uneasiness tended to be greater in the VG (P=0.127); however, this index decreased in both groups in a similar manner (Table 3). The STAI A-State (condition for uneasiness) reflects a temporary conditional uneasiness for stress: 42 points in both males and females shows high conditional uneasiness, which was observed in 21.4% and 21.4% of the VG and NG, respectively. This score tended to be lower in the VG than in the NG at week 2 (34.50±9.37 vs 37.36±4.85, respectively, P=0.160), and a significant decrease was seen at 4 and 12 weeks in the VG, but not the NG.

Table 5. Changes in Body Weight and Vital Signs Over 12 Weeks

Item	Time point	Varenicline (n=14)	Nicotine patch (n=14)	Z	P value
Weight	First visit	67.29±9.03]**	66.19±13.30]**	−0.414	0.679
	Week 12	69.18±9.63]**	68.27±13.40]**	−0.505	0.613
BMI	First visit	23.72±3.26]**	23.59±3.64]**	−4.590	0.646
	Week 12	24.38±3.42]**	24.37±3.72]**	−0.551	0.581
Change in body weight from the first visit to 12 weeks		1.89±2.10	2.08±2.00	−0.207	0.836
Body temperature	First visit	36.56±0.35	36.86±0.42]*	−1.667	0.095†
	Week 12	36.51±0.48	36.54±0.45]*	−0.023	0.981
Pulse rate (/min)	First visit	78.50±10.55]*	76.57±7.95]†	−0.301	0.764
	Week 12	72.57±8.72]*	71.36±11.93]†	−0.162	0.871
SBP (mmHg)	First visit	126.9±15.57	131.1±19.63	−1.036	0.300
	Week 12	126.4±15.75	124.4±15.61	−0.437	0.662
DBP (mmHg)	First visit	77.43±10.56	78.36±10.05	−0.601	0.548
	Week 12	75.64±11.35	78.21±10.54	−0.806	0.420

Data are mean±SD. Mann-Whitney test: †P≤0.1, *P≤0.05, **P≤0.01.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 6. Characteristics and Smoking History of Successful and Unsuccessful Cases of Abstinence

Characteristics	Continuous abstinence (n=21)	Continuous smoking (n=7)	Z	P value
Age (years)	46.05±11.84	46.14±12.19	−0.159	0.873
Sex				
M(n)/F(n)	17 (81.0)/4 (19.0)	6 (85.7)/1 (14.3)		
Weight (kg)	67.1±12.68	65.8±4.9	−0.345	0.730
BMI	23.73±3.78	23.45±1.98	−0.133	0.894
Age smoking started (years)	18.1±2.32	19.71±2.22	−1.409	0.159
Duration of smoking (years)	26.57±10.98	25.29±11.90	−0.186	0.853
Cigarettes smoked per day	24.05±7.85	34.29±10.18	−2.632	0.009**
Brinkman index	640.95±368.10	885.00±524.08	−1.194	0.232
TDS score	7.57±1.60	7.71±1.50	−0.162	0.871
Previous smoking abstinence experience (%)	15 (71.4)	5 (71.4)		
Previous use of nicotine patch (%)	2 (9.5)	–		
Previous use of nicotine gum (%)	2 (9.5)	1 (14.3)		
End-expiratory CO conc. (first visit) (ppm)	22.86±9.61	37.86±7.93	−3.295	0.001***
STAI trait anxiety (first visit)	41.90±8.31	41.14±5.43	−0.292	0.770
STAI state anxiety (first visit)	37.71±6.89	37.86±8.32	−0.293	0.770
SCL (first visit)	5.67±4.29	4.57±2.57	−0.482	0.630

Data are mean±SD. Mann-Whitney test: †P≤0.1, *P≤0.05, **P≤0.01, ***P≤0.001.
BMI, body mass index; Brinkman index, cigarettes per day×smoking history (years); TDS, Tobacco Dependence Screener; STAI, State-Trait Anxiety Inventory; SCL, Stress Check List.

Safety and Adverse Effects Self-monitored symptoms and side-effects are listed in Table 4. The number of side-effects was greater in the VG than in the NG (43 vs 23, respectively). No difference was observed in laboratory data (5 and 6 cases, respectively). Adverse effects were classified as gastrointestinal disorders [14 (87.5%) in VG vs 1 (6.3%) in NG], psychological disorders [8 (50.0%) and 3 (18.8%), respectively], especially insomnia [6 (37.5%) and 2 (12.5%), respectively] or nausea [4 (25%) only in VG]. Skin symptoms, especially an itchy feeling, were seen in 9 (56.3%) in the NG. Laboratory examinations showed almost no changes, except that uric acid slightly increased in 1 case in each group, and γGTP increased in 2 cases and 1 case, respectively. Non-specific ECG abnormality was observed in the NG, but these changes were all mild, within normal limits, and not clinically important.

Vital Signs and Body Weight

Body temperature, pulse rate, and blood pressure are shown in Table 5. Body weight and BMI were increased after 12 weeks in the VG and NG [13 cases (92.7%) and 12 cases (85.7%), respectively]. The mean body weight increase was 1.89 kg and 2.08 kg, respectively, and blood pressure did not change in either group. Systolic blood pressure was similar between the 2 groups. Body temperature significantly decreased between before and at 12 weeks in the NG (36.86±0.42 vs 36.54±0.45, respectively, $P<0.05$), and pulse rate significantly decreased between before and at 12 weeks in the VG (78.5±10.55/min vs 72.57±8.72/min, respectively, $P<0.05$); however, these changes were within normal ranges.

Discussion

This is the first head-to-head trial of varenicline and nicotine patch for the cessation of smoking in Japan. The continuous abstinence rates at weeks 9–12 and 9–24 were almost equal, but there was a greater incidence of adverse effects in the VG than in the NG (42 vs 23 adverse events, 29 vs 16 adverse drug actions, respectively). There also tended to be a greater incidence of withdrawal symptoms in the VG. Among the continuous abstinence cases, the total withdrawal symptom score (MNWS) in the VG tended to be higher than that in the NG at 2 weeks (14.80±3.49 vs 12.18±2.44, P=0.083, data not tabulated), which might be related to VG adverse events. The Food & Drug administration reported that during smoking cessation, nicotine withdrawal symptoms that are similar to psychiatric adverse events may be experienced in some patients taking varenicline and that these symptoms stopped after varenicline was discontinued,[11] suggesting the drugs themselves are triggering the symptoms.

The items that reflected a realization of the effects of non-smoking were significantly increased in the NG during the 12 weeks, but no changes were observed in the VG (Table 3). However, the STAI A-State (condition for uneasiness) showed that high conditional uneasiness scores were decreased in the VG, and were stable or increasing at week 8 in the NG. At the time of the study the nicotine patch had been approved for only 8 weeks in Japan, which may have affected the responses by the patients in the NG.[9]

Two comparative studies of varenicline and nicotine patch have been performed previously,[12,13] and both showed that smoking abstinence rates were greater with varenicline. We reviewed these articles, and found some differences from our protocol. First, the duration of nicotine patch treatment was 10 weeks in the Western countries, whereas it was 8 weeks in Japan[9] and in this current trial. The nicotine patches used in Western countries contained 21, 14, and 7 mg/patch for high, medium and mild doses, whereas these values were 52.5, 35, and 17.5 mg, respectively, in our trial. Second, in our study, the frequency of previous use of nicotine patch and gum were far less than in Western countries (1–3% in this trial vs 46–49% in Western countries). The results of questionnaires obtained from 3,600 smokers in Japan showed that only a few had received anti-smoking guidance or instruction and, among them, 70% of males had received nicotine replacement therapy, 47% of females had been treated with a nicotine patch, and far fewer had received nicotine gum. These findings indicate that very few had received medical treatment to help them stop smoking, even though 50% of patients with hypertension or hyperlipidemia are usually treated in a hospital. These differences may explain some of the differences between our results and the other findings in Western countries, and should be explored further.

Overall, in our study 21 patients stopped smoking regardless of the stop-smoking intervention, while 7 failed to stop smoking at 12 and 24 weeks. The characteristics of the successful and unsuccessful groups are compared in Table 6. The number of cigarettes smoked and the end-expiratory CO concentration at baseline were smaller in the successful group than in the unsuccessful group (24.05±7.85/day vs 34.29±10.18/day, P=0.009; 22.86±9.61 ppm vs 37.86±7.93 ppm, P=0.001, respectively), and the age at which smoking started tended to be younger in the successful group than in the unsuccessful group (18.10±2.23 years vs 19.71±2.22 years, P=0.159, respectively). In Japan, among current and former smokers the males started smoking at approximately 17 years, and females started at 18 years but there was no difference in the sex distribution in this trial.

The current data indicate that heavy smokers quit smoking at only a low frequency and the final smoking abstinence rates were similar between treatment with varenicline and a nicotine patch with tolerable adverse effects, which means that the choice of drugs should depend on the patient's request.

Cigarette smoking relates to cardiovascular (CV) risk,[14,15] and smoking cessation reduces the CV risk. With regard to primary prevention, excess CV risk is reduced by 35–50% in 2 years, and is completely gone in 10–15 years. Modest changes in CV risk factors have contributed to considerable reductions in the incidence of myocardial infarction (MI). Hardoon et al in the UK reported that the decline in cigarette smoking explained 23% (approximate 95%CI 15–34%) of the observed 62% decline in the hazard of MI over the 25 years from baseline.[16] Effective tobacco treatment is available and is very cost-effective.[17] Treatment of smoking is the standard of care for CV risk reduction, but interventions without follow-up are not effective, especially for adult smokers.[18] Therefore, long-term management is needed, as in the standard treatments for hypertension, hyperlipidemia and metabolic syndrome.

Study Limitations

This was the first randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers in Japan, but the study population was too small and the study duration was only 24 weeks. Long-term monitoring is needed. In addition, we did not account for the effect of passive smoking.

We conclude that the selection of treatment should depend on the patient's request based on the balance of desired acuteness of cessation of smoking and withdrawal symptoms or side-effects, such as gastro-intestinal problems or skin allergy.

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