Clonidine for Smoking Cessation

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Abstract

Clonidine was used to reduce withdrawal symptoms of nicotine and increase the success rate of smoking cessation in the smoking cessation clinic of Siriraj Hospital. One hundred and fourteen subjects enrolled in a double-blind, randomised, placebo-controlled trial. Subjects were divided as clonidine group (n=58) with the mean age of 38 years and placebo group (n=56) with the mean age of 33 years. Both groups received information about harmful effects of smoking as well as behavioral modification protocol. The dose of clonidine used in this study was 300 microgram and the duration of the trial was 5 weeks. Both subject groups attended the clinic weekly and received identical counselling. Clonidine did not reduce withdrawal symptoms of nicotine when compared to the placebo and the success rate of smoking cessation at the end of the 5 weeks' period was identical between the two groups (clonidine 50%; placebo 48%, $p>0.05$). No significant side effects of clonidine were found. There was no correlation between background educational level, income, amount of cigarettes smoked per day and the success rate in both groups. In conclusion, clonidine did not show any beneficial effect on smoking cessation.

Cigarettte smoking is still the chief cause of preventable death. In Thailand 10.4 million people or approximately 18 per cent of the population are smokers. Each year 42,000 Thai die from smoking-related illnesses(1).

Smoking is a complex and highly addictive activity. Tobacco smoke is a complex substance containing a multitude of different chemicals. The peripheral effects of nicotine which is the most important of the 3,800 substances in cigarette smoke are well known. These include increased heart rate, vasoconstriction, elevation of blood sugar level and relaxation of peripheral muscle. Nicotine is a highly addictive drug(2). One third to one half of occasional cigarette smokers graduate to maladaptive use and to physical dependence of nicotine(3,4). Addiction can be defined as the compulsive use of a psychoactive drug and is associated with a triad of compulsion, tolerance and a withdrawal syndrome. The vast majority of people

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who quit smoking relapse within days[5,6]. It is in this area that drug therapy has a role to play in smoking cessation.

The alpha-2-noradrenergic agonist, clonidine, has been used successfully to aid opiate and alcohol withdrawal and a recent study has suggested that it may have a role in smoking cessation[7]. We report the results of a randomised, double-blind, placebo-controlled study evaluating the effects of clonidine on smoking cessation.

SUBJECTS AND METHOD

Subjects

The clinical trial was conducted at the smoking cessation clinic, Siriraj Hospital, Bangkok. Participants were recruited by notices posted at the out-patient building as well as advertisements in newspapers and radio. Subjects over 15 years of age who had smoked regularly for a minimum of one year were eligible. Exclusion criteria were as follows: 1) any preexisting medical condition, 2) current use of nicotine gum, 3) history of alcohol or other substance abuse, 4) known allergy to clonidine, 5) pregnancy or lactation, 6) hypertension being treated with any adrenergic agent.

Protocol

Smokers were enrolled as groups of 15 to 30 people. The study procedure was explained by an investigator. Informed consent was obtained. Measurements of blood pressure (supine & standing), pulse rate were taken. At the initial visit, all smokers received behavioral counselling. Specific guidance was offered (Table 1). During the first week of the study, while continuing to smoke, subjects took 75 micrograms tablet of clonidine hydrochloride or placebo in randomised, double-blind fashion and increased the dosage by one tablet every other day. By the end of the first week every subject was taking two tablets twice a day (300 micrograms per day). Subjects attended a follow-up meeting at 1 week. They were interviewed for any side effects of clonidine by using visual analogue scale. The following day was quit day. Subjects continued to receive the full dose of medication for 3 weeks and then tapered by one tablet every other day during the ensuing week.

Subjects were seen by investigators weekly to encourage continued abstinence or attempts to quit, to assess and analyse their smoking diaries. Symptoms of nicotine withdrawal were also evaluated using visual analogue scale. Compliance was assessed by tablet count and self-report as well as an ability to provide follow-up information. In analyses, dropouts were considered to be smokers. Comparisons between groups were done using chi-square or Student's *t* tests as appropriate.

Table 1. Strategies for helping a patient quit smoking.

a. provide positive orientation about quitting
b. promote negative thoughts about smoking
c. discuss method of cessation - cold turkey approach
d. urge patient to set quit date in advance
e. identify triggers to smoking with aid of smoking diary
f. suggest substitute activities eg. chewing gum and/or avoidance schemes.
g. anticipate withdrawal symptoms
h. discuss weight gain
i. set up reinforcement system
j. schedule follow-up visits

RESULTS

Baseline characteristics of the 114 smokers enrolled were shown in Table 2. There were 58 patients receiving clonidine and 56 received pla-

Table 2. Baseline characteristics of subjects

Characteristic	Clonidine	Placebo
No. of subjects	58	56
Age,* yr. (± S.D.)	38.8±14.2	33.2±13.4
range, yr	15-80	15-75
Male: Female	50:8	49:7
Education level		
Primary & Secondary (%)	21 (36.8)	12 (21.4)
High School (%)	21 (36.8)	31 (55.4)
Tertiary (%)	16 (26.4)	13 (23.2)
Income		
<5000 B/m (%)	39 (69.6)	33 (58.9)
5000-12000 B/m (%)	11 (19.6)	16 (28.6)
>12000 B/m (%)	6 (10.7)	7 (12.5)
Cigarettes/d		
1-10 (%)	19 (33.3)	16 (31.4)
10-20 (%)	17 (29.8)	20 (39.2)
>20 (%)	21 (368)	18 (29.4)
Years of smoking ± S.D.	20.0±11.8	14.9±10.4
range	2-50	1-40
Previous attempt to quit (%)	12 (20.7)	13(23.2)
Other smokers in house hold (%)	29 (50.0)	24 (43.6)

* $p<0.05$; B = baht (US$ 1.0≈baht 27.0)

Table 3. Success rates at end of five weeks.

	Clonidine	Placebo	p
No. of subjects	58	56	
Successful quitters (%)	29 (50.0)	27 (48.2)	NS
Reduce average number of cigarettes per day ≥50%	4 (6.9)	4 (7.1)	NS
Unsuccessful quitters (%)	9 (15.5)	13 (23.2)	NS
Loss follow-up	16 (27.6)	12 (21.4)	NS

NS = not significant, $p > 0.05$

Table 4. Stratified analysis of success rates at end of five weeks.

	Success/total (%)		p
	Clonidine	Placebo	
Education level			
low n=22	10/13 (76.9)	4/9 (44.4)	NS
high n=64	23/29 (79.3)	27/35 (77.1)	NS
Income			
low n=51	18/25 (72.0)	19/26 (73.1)	NS
high n=34	14/16 (87.5)	12/18 (66.7)	NS
No. of cigarettes per day			
<15 cig/d n=25	9/12 (75.0)	9/13 (69.2)	NS
>15 cig/d n=55	23/29 (79.3)	18/26 (69.2)	NS

NS = not significant, $p > 0.05$

Table 5. Visual analogue scale of withdrawal symptoms at day 14 (7 days after quit day).

	Clonidine n=28	Placebo n=17	p
Headache	1.14±2.21	1.06±1.64	NS
Irritable/upset	2.54±2.60	2.71±2.93	NS
Trouble concentrating	1.21±2.41	2.18±2.83	NS
Hunger	2.07±2.48	3.47±3.66	NS
Craving	3.36±2.26	4.59±2.92	NS

NS = not significant, $p > 0.05$
Scores are the means ± SD

cebo. There were no significant differences in sex, education, income, average number of cigarettes per day or number of years subjects smoked between the clonidine and placebo group. Smokers in the clonidine group were significantly older (38.8± 14.2 years) than the placebo group (33.2±13.4 years; $p < 0.05$). At the end of five weeks, only 86 subjects enrolled were available for follow-up (clonidine 42; placebo 44). Table 3 illustrated the relationship between study group and smoking status at five weeks. No statistically significant effect of clonidine could be demonstrated. Fifty per cent of the subjects in the clonidine group and 48.2 per cent of the placebo group successfully quit their smoking ($p>0.05$). Successful quit rates were further analysed in both groups by comparing education level (primary education *vs* high school or higher): level of income per month (<5,000 Baht *vs* >5,000 Baht); number of cigarettes smoked per day (<15 cig/d *vs* >15 cig/d). These factors had no effect on the success of smoking cessation (Table 4). Table 5 shows the mean withdrawal symptom scores at day 14 of the study (7 days after quit day). Only 45 subjects, 28 in the clonidine and 17 in the placebo group, were available for follow-up at day 14. Withdrawal symptoms measured included headache, irritability, impairment of concentration, hunger and craving. These symptoms were not different between both groups. Side effects of clonidine were generally mild and were not significantly different from the placebo group (Table 6). Supine systolic blood pressure as well as systolic and diastolic blood pressure in upright position were significantly

Table 6. Adverse events.

Symptoms	Clonidine n=43		Placebo n=35	
	VAS $\bar{x}$±SD	Median (range)	VAS $\bar{x}$±SD	Median (range)
Drowsiness	3.09±3.21	3(0-9)	2.57±2.32	3(0-9)
Dry mouth	3.23±2.79	3(0-9)	2.46±2.53	2(0-9)
Lightheadedness	1.49±2.50	0(0-9)	1.89±2.65	0(0-9)
Headache	1.02±2.30	0(0-9)	0.69±1.53	0(0-9)
Increased appetite *	2.23±2.75	0(0-9)	4.03±3.89	5(0-9)
Insomnia*	0.54±1.61	0(0-9)	1.97±2.86	0(0-9)

* $p<0.05$
VAS = visual analogue scale
Scores are the means ± SD

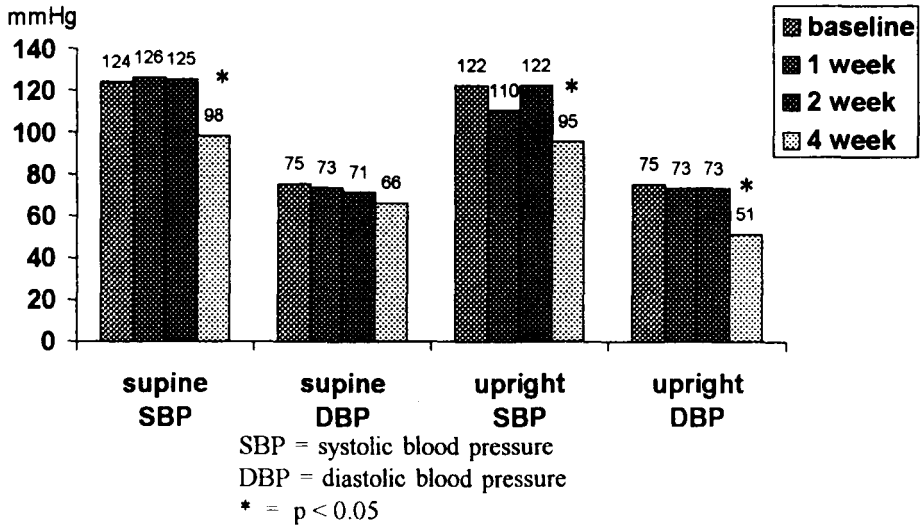


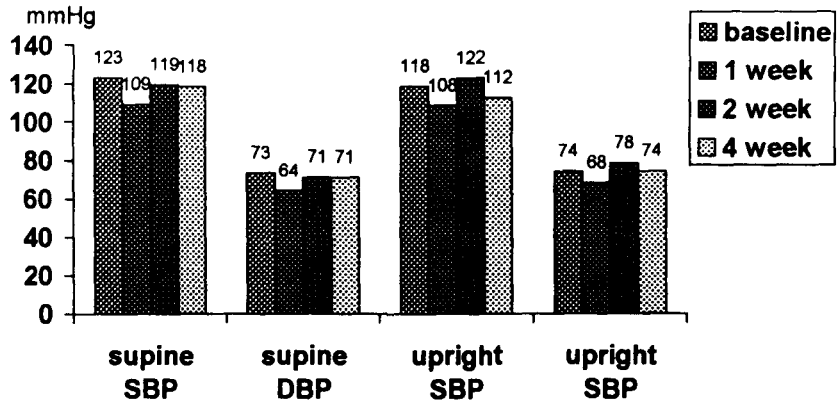
Fig. 1 Supine & upright blood pressure in clonidine group.

reduced in the clonidine group at week four of treatment compared to baseline values (Fig. 1). Blood pressure in the placebo group did not change during the study (Fig. 2).

DISCUSSION

This five week controlled trial showed no beneficial effect of clonidine on reducing withdrawal symptoms during cessation of smoking. Furthermore no statistically significant effects on quitting were found at 5 weeks.

In 1984, Glassman et al[7] reported that clonidine, an alpha-agonist widely used for hypertension was significantly more effective than either placebo or a benzodiazepine in reducing symptoms during acute withdrawal from tobacco. These results prompted several placebo-controlled trials to test the efficacy of clonidine as an aid for achieving smoking cessation[8-15]. Findings from these studies, however, have not been uniform. A favorable clonidine effect was observed in some studies, while no measurable benefit from clonidine was reported in others. Franks P. et al[10] enrolled 185 subjects, 92 receiving clonidine and



SBP = systolic blood pressure
DBP = diastolic blood pressure

Fig. 2 Supine & upright blood pressure in placebo group.

93 receiving placebo, in a randomised, double blind study of clonidine for smoking cessation in a primary care setting. Clonidine had no demonstrable effect on withdrawal. At 4 weeks, 18 per cent receiving clonidine had quit compared with 14 per cent receiving placebo. Glassman et al[8] conducted a four-week controlled trial of clonidine as an aid in short term smoking cessation. More than twice as many smokers receiving clonidine were successful compared with those receiving placebo (61% *vs* 26%). This difference is the result of the strong effect of the drug on women, while men showed virtually no difference in effect between active drug and placebo. In the present study over 80 per cent of the subject were men. This may be one explanation why we could not repeat Glassman's observation. However, Hao & Derson's[15] positive result with a largely male sample, suggested that clonidine may benefit men as well. In previous reports[8-16] the mean short term success rate of clonidine for smoking cessation was 39 per cent (range 18 - 70%) compared with 21 per cent of placebo (range 9 - 53%). These studies varied in several treatment characteristics, for example, specialized smoking clinics *vs* general practice settings, oral medications *vs* transdermal patch, dosage range (0.1-0.45 mg/day), treatment period which varied from 2 to 12 weeks (majority 3-6 weeks duration) and lastly with or without behavioral counselling. In our study all subjects went through group conselling and individual behavior therapy. This process certainly has influence on the very high success rate in the placebo group (48%) and showed only a small non significant relative effect of clonidine (50%). Another reason for the very high success rate in the placebo group is the level of motivation. These patients presented specifically for smoking cessation so they were highly motivated to active successful smoking cessation. The high success rate in the placebo group was also observed by Murray et al[14] who achieved a high placebo quit rate (53%) and also a high clonidine success rate (58%). This study also added adjunctive behavior group counselling in their protocol and resulted in this extraordinary placebo rate. Covey and Glassman[16] performed a meta-analysis of nine randomized double-blind placebo controlled trials previously reported on clonidine and found that the most impressive difference was observed between studies that employed behavioral therapy and those that did not. Combined results from nine trials, that all together entered 813 subjects, showed that the success rate with clonidine was significantly greater than the proportion of successes with placebo (39% *vs* 21%, $p<0.001$). The common odds ratio was 2.36, 95%

confidence interval = 1.69-3.28, indicating that the odds of stopping smoking with clonidine was more than twice the odds of stopping smoking with placebo.

Another subject characteristic that requires consideration when evaluating clonidine efficacy is the level of nicotine dependence. Clonidine's advantage over placebo was greater among smokers more dependent on tobacco as measured by the Fagerstrom Tolerance Questionnaire[17]. Highly dependent smokers are, typically, heavy users of tobacco who smoke within a few minutes after awakening[9]. Such data were unavailable in our study. The only evidence we had regarding nicotine dependence was the number of cigarettes smoked per day (Table 2) which was similar in both groups.

As with all addictions, even in smokers succeeding in short-term cessation, they run a high risk of relapse. Relapse rates are high throughout the first three months after smoking cessation[18]. One-year success rates for most smoking cessation programs are less than 20 per cent[8].This five-week experiment was designed to examine short-term cessation and thus limited insight on the long-term outcome of clonidine treatment.

Of pharmalogic approaches to smoking cessation, nicotine replacement therapies have shown some promise. The rates of cessation during the first few months of treatment with transdermal nicotine preparations typically range from 20 to 40 per cent[19,20]. These rates are about twice those achieved by patients given placebo and three times those of patients who try to quit smoking without any form of therapy[2]. Treated patients remain susceptible to relapse and the long term efficacy is usually lower. In one study in a general practice setting, the rates of abstinence in the nicotine and placebo groups at two years were 12 and 3 per cent, respectively[21]. In studies of nicotine polycrilex, the benefit of treatment, compared with placebo, was significant at six months but equivocal at one year[22,23].

However, the costs of nicotine patch and nicotine gum in this part of the world are still very high and unaffordable to the majority of smokers. Observations suggested that a high percentage of subjects who successfully stopped smoking were still using nicotine gum at six months[24].

The most frequently observed side effects of clonidine was drowsiness and dry mouth. In this study, adverse symptoms were equally distributed in both the clonidine and placebo group (Table 6). Even though blood pressure was lowered with clonidine after four weeks of treatment (Fig. 1), none of the subjects discontinued clonidine prematurely due to this effect.

Even though meta-analysis has provided encouraging findings for the acute treatment of nicotine dependence with clonidine, our results do not support the use of clonidine for smoking cessation. We have shown that conjunctive use of behavioral therapy may modify clonidine response.

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การใช้ยาโคลนิดีน เพื่อช่วยอดบุหรี่

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คณะผู้วิจัยได้ทำการศึกษาผลของยา clonidine ชนิดเม็ดเพื่อช่วยอดบุหรี่ในคลินิกอดบุหรี่ของโรงพยาบาลศิริราช ด้วยวิธี randomised, double-blind, placebo controlled trial มีผู้ประสงค์จะอดบุหรี่เข้ารับการรักษาจำนวน 114 คน แบ่งเป็นกลุ่มที่ใช้ยา clonidine 58 คน มีอายุเฉลี่ย 38 ปี และยาหลอก 56 คน อายุเฉลี่ย 33 ปี ผู้อดบุหรี่ทั้งหมดได้รับความรู้เกี่ยวกับพิษภัยของบุหรี่และผลดีที่จะได้รับเมื่ออดบุหรี่ได้ เพื่อเสริมความตั้งใจของผู้อดบุหรี่ในกลุ่ม และคำแนะนำเกี่ยวกับวิธีการปรับเปลี่ยนพฤติกรรมการสูบบุหรี่ ขนาดของยา clonidine ที่ใช้คือ 300 มคก./วัน หรือยาหลอกเป็นเวลา 5 สัปดาห์ ปรากฏว่า clonidine ไม่ช่วยลดอาการของการขาดนิโคติน รวมทั้งไม่ช่วยให้อดบุหรี่สำเร็จมากขึ้นเมื่อเทียบกับยาหลอก (clonidine 50% ยาหลอก 48%, p >0.05) การศึกษานี้ไม่พบผลข้างเคียงที่สำคัญจากการใช้ยา clonidine ปัจจัยต่างๆได้แก่ระดับการศึกษา, รายได้ต่อเดือน, จำนวนบุหรี่ที่สูบต่อวัน ไม่มีผลต่อความสำเร็จของการอดบุหรี่

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