



No association between low-dose reserpine use and depression in older hypertensive patient: result of a multicenter, cross-sectional study

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Abstract

Background Reserpine is currently used by millions of Chinese hypertensive patients, in spite of the continued concern of its depressogenic effect, even when used in low dose. This study aimed to investigate the association between low-dose reserpine use and depression in older Chinese hypertensive patient. **Methods** In this cross-sectional, case-control study, we recruited patient aged 60 years or over who had regularly taken one or two tablets of “compound reserpine and triamterene tablets (CRTTs)” for more than one year (reserpine user) from 26 community health centers located in 10 provinces in China. For each patient who took CRTTs, we selected an age (within five years) and sex matched hypertensive patient who had never taken any drugs containing reserpine (non-reserpine user) as control. Depressive symptoms were evaluated using a Chinese depression scale adapted from the Zung Self-Rating Depression Scale. Demographic, clinical data and laboratory examination results within six months were collected. **Results** From August 2018 to December 2018, 787 reserpine user and 787 non-reserpine user were recruited. The mean age of all study subjects was 70.3 years, with about equal numbers of males and females. The mean depression score was 40.4 in reserpine users and 40.6 in non-reserpine users ($P = 0.7$). The majority of study subject had a depression score < 53 (87.6% in reserpine users and 88.2% in non-reserpine users, respectively). There were no significant differences in the prevalence of mild, moderate or severe depression in reserpine users and non-reserpine users. **Conclusions** There is no association between low-dose reserpine use and depression in older hypertensive patient. The role of reserpine in the treatment and control of hypertension should be re-considered; and further studies, especially randomized, controlled clinical trials to compare efficacy and safety of reserpine and other widely recommended anti-hypertensive agents are needed.

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1 Introduction

Reserpine, an alkaloid extracted from the root of *Rauwolfia serpentina* which was introduced to modern medicine in the mid-1940s, was one of the earliest drugs used to treat hypertension.^[1] Reserpine binds to the storage vesicles in adrenergic neurons and inhibits the uptake of norepinephrine and dopamine, which leads to their degradation by cytoplasmic monoamine oxidase, and thus reduces cardiac output and peripheral resistance.^[1]

Randomized, placebo-controlled clinical trials conducted in western countries from 1960s to 1990s had continuously demonstrated the powerful blood pressure (BP) lowering effect of reserpine, when combined with thiazide diuretics and hydralazine,^[2,3] or combined with thiazide diuretics alone.^[4-7] More recently, reserpine was included as one of the optional step 2 agents in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.^[8] At five years, reserpine was used by 4.3% of subjects and showed similar, or perhaps better results in reducing BP and cardiovascular events, when compared with atenolol or clonidine.^[8]

Despite the dramatic decrease to near demise of reserpine use since the 1980s in westernized countries, partly attributed to several adverse effects of reserpine reported in studies conducted in the 1950s to 1970s, which included depression, gastric bleeding, and breast cancer.^[9] In China, however, reserpine is still used extensively in the treatment of hypertension, usually at low dose and as an ingredient in fixed-dose compounds. Recent local and nation-wide surveys indicate that about 5 millions to 20 millions of Chinese patients with hypertension are using reserpine as one of the treatment medications.^[10-12]

In the Hypertension Detection and Follow-Up Program, 1036 of patients were treated with reserpine. Authors of this study concluded that there was no evidence that reserpine cause breast cancer;^[13] another large-size study with low-dose reserpine showed no increase of gastric bleeding.^[14] Concern of the association of depression and reserpine use, however, is continued.^[15] Therefore, we performed this multicenter, cross-sectional study to investigate the association between low-dose reserpine use and depression in elderly Chinese hypertensive patient.

2 Methods

2.1 Study subjects

This cross-sectional, case-control study was conducted from August 2018 to December 2018. We invited 26 community health centers (CHC) located in 10 provinces in

China, including Beijing, Tianjin, Henan, Anhui, Shandong, Shanxi, Sichuan, Liaoning, Jiangsu and Hebei, to participate in this study. The Ethics Committee of Xuanwu Hospital Capital Medical University approved the study protocol (Clinical Trial Number: ChiCTR1800017684). All subjects provided written informed consent.

The most widely used fixed-dose compound containing reserpine for the treatment of hypertension in China is the “compound reserpine and triamterene tablets (here referred to by its acronym, CRTTs)”. Each table of CRTTs contains hydrochlorothiazide 12.5 mg, triamterene 12.5 mg, dihydralazine 12.5 mg and reserpine 0.1 mg. Previous study had confirmed the efficacy of this compound in treating hypertensive Chinese patients.^[16] Thus, we recruited patient aged 60 years or over who had regularly taken one or two tables of CRTTs for more than one year in this study. For each patient who took CRTTs (reserpine user), we randomly selected from the same CHC an age (within five years) and sex matched hypertensive patient who had never taken any drugs containing reserpine (non-reserpine user) as control. By the end of December 2018, 828 pairs of CRTTs patient and control had been recruited. We excluded 41 pairs with incomplete clinical data. Finally, 787 pairs of CRTTs patient and control were included in the analysis.

We assumed that patient at advanced age maybe more susceptible to the depressogenic effect of reserpine; thus, in this study, we also specifically compared the depression status reserpine user and non-reserpine user in those subjects aged 80 years or over.

2.2 Demographic and clinical data collection

Demographics and clinical data were gathered, including gender, age, height, weight, waist circumference, history of hypertension and other diseases, medication use, and laboratory examination results within six months, including concentrations of plasma sodium and potassium, serum creatinine and urea nitrogen, fasting blood glucose and plasma lipid profiles were collected.

2.3 Depressive symptoms assessment

Depressive symptoms were evaluated using a Chinese depression scale adapted from the Zung Self-Rating Depression Scale.^[17] The Chinese depression scale used in our study has been validated previously.^[18,19] This self-rating depression scale consists of 20 statements about feelings and symptoms of depression, such as sleep and appetite. Each statement is rated by the participant on a 4-point scale, ranging from a little of the time to most of the time. Total scores were multiplied by 1.25 to given a final scale ranging from 25 to 100, with higher scores indicating more depres-

sive symptoms. In this study, we used the following cutoffs for the classification of depression severity: < 53: no depression; 53–62: mild depression; 63–72: moderate depression; and ≥ 73 : severe depression, according to Chinese norms.^[20]

2.4 Statistical analysis

Statistical analyses were performed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean \pm SD and compared using Student *t* test or Mann–Whitney U test. The categorical data were presented as percentage frequency (%) and compared using chi-squared test. A two-tailed $P < 0.05$ indicates statistical significance.

3 Results

3.1 Characteristics of patients with or without the use of reserpine

The demographic and clinical characteristics of patients who used CRTTs and those who did not use any reserpine-containing anti-hypertensive agents are shown in Table 1. The mean age of all study subjects was 70.3 years, with about equal numbers of males and females. There were no significant differences between reserpine users and non-reserpine users in duration of hypertension, systolic and diastolic blood pressure and laboratory variables. Compared to those non-reserpine users, patients who used CRTTs took less mean number of anti-hypertension medication tables per day (1.3 vs. 1.4, $P = 0.021$).

Table 1. Clinical characteristics of reserpine user and non-reserpine user.

	Reserpine user (<i>n</i> = 787)	Non-reserpine user (<i>n</i> = 787)	<i>P</i> -value
Age, yrs	70.4 \pm 7.4	70.1 \pm 6.9	0.365
Male/Female	392/395	392/395	-
BMI, kg/m ²	25.5 \pm 3.4	25.4 \pm 3.6	0.633
Waist circumference, cm	88.3 \pm 10.6	88.0 \pm 10.7	0.614
Duration of hypertension, yrs	12.2 \pm 9.8	11.5 \pm 9.5	0.158
Type 2 diabetes	166 (22.0%)	189 (24.0%)	0.165
Coronary heart disease	219 (27.8%)	214 (27.2%)	0.778
Stroke	129 (16.4%)	108 (13.7%)	0.139
Hypertension grade			0.467
1	284 (36.1%)	294 (37.5%)	
2	221 (28.1%)	234 (29.5%)	
3	282 (35.8%)	259 (33.0%)	
Systolic BP, mmHg	137.1 \pm 16.1	138.7 \pm 16.5	0.057
Diastolic BP, mmHg	80.3 \pm 10.2	81.3 \pm 10.8	0.061
Number of anti-hypertension medication table per day	1.3 \pm 0.6	1.4 \pm 0.6	0.021
Patient who use other anti-hypertension medication			
CCB	129 (16.4%)	552 (70.1%)	< 0.001
ACEI	32 (4.1%)	93 (11.8%)	< 0.001
ARB	75 (9.5%)	269 (34.2%)	< 0.001
β blockers	34 (4.3%)	103 (13.1%)	< 0.001
Diuretics	13 (1.7%)	54 (6.9%)	< 0.001
Others	7 (0.9%)	3 (0.4%)	0.204
Serum creatinine, μ mol/L	78.9 \pm 35.6	76.8 \pm 30.6	0.213
Serum urea nitrogen, mmol/L	6.1 \pm 2.4	5.9 \pm 1.9	0.128
Fasting glucose, mmol/L	6.2 \pm 1.9	6.3 \pm 2.2	0.204
Triglycerides, mmol/L	1.8 \pm 1.3	1.8 \pm 1.3	0.981
Total cholesterol, mmol/L	4.8 \pm 1.2	4.9 \pm 1.2	0.171
HDL-cholesterol, mmol/L	1.4 \pm 0.4	1.4 \pm 0.4	0.688
LDL-cholesterol, mmol/L	2.8 \pm 0.9	2.8 \pm 0.9	0.307
Potassium, mmol/L	4.2 \pm 0.5	4.2 \pm 0.5	0.115
Sodium, mmol/L	140.5 \pm 8.9	140.6 \pm 9.6	0.909

Data are presented as means \pm SD or *n* (%). ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CCB: calcium channel blocker; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

3.2 Depressive symptoms in patients with or without the use of reserpine

The mean depression score was 40.4 in reserpine users and 40.6 in non-reserpine users ($P = 0.7$). The majority of study subject had a depression score < 53 (87.6% in reserpine users and 88.2% in non-reserpine users, respectively). There were no significant differences in the prevalence of mild, moderate or severe depression in reserpine users and non-reserpine users (Table 2).

3.3 Depression status in patients 80 years or older

There were 102 subjects who were 80 years or older in reserpine users and 83 in non-reserpine users. There were no significant differences in either the mean depression score or the prevalence of mild, moderate or severe depression between the two sub-groups (Table 3).

4 Discussion

In this large scale, multicenter, cross-sectional study of elderly hypertensive patients, we found that compared with patients who took no reserpine, patients who had took low dose (0.1–0.2 mg/d) reserpine for one year or longer showed similar depressive symptom score and similar prevalence of mild, moderate or severe depression, while both systolic and diastolic BP were also similar between the two groups.

To our knowledge, the only previous study specifically addressed the relationship between reserpine use and depression was reported by Lemieux and associates.^[21] In their

study, 195 patients took Rauwolfia products, of them 134 took reserpine alone, and 101 patients took no Rauwolfia products. Of the 101 patients in that study who took no Rauwolfia or reserpine, none reported developing depression. Of the group that took Rauwolfia products, 30 of 195 patients reported developing depression. The daily dosage of reserpine used in their studied patients was 0.75 to 4 mg, with an average of 1.36 mg, much larger than the dosage used in our studied subjects. Several later studies in which low dosages (0.05–0.1 mg/d) of reserpine are used showed that reserpine is well tolerated and that depression develops at rates similar to those seen in the general population.^[16,22,23] Although the dose-related hypotensive effect of reserpine needs further investigation,^[24] a randomized trial showed that doses of 0.125 mg and 0.05 mg produced 90% and 82% of the BP reduction of the standard dose (0.25 mg) when all doses were combined with chlorthalidone 25 or 50 mg.^[25]

The study by Liao, *et al.*^[15] claimed that reserpine use is a risk factor of depression (OR = 6.667, 95% CI: 1.981–22.43) in hypertensive patients. However, in their study, the dosage of reserpine was not reported; furthermore, we found the some of the data presented in this report is hard to explain after careful examination.

We believe the results of our study have important clinical implications. Both hypertension and depression are leading contributors to the global disease burden in China. Considering that millions of Chinese hypertensive patients are taking reserpine-containing compounds as their treatment medication, if there do exist an association between reserpine use and the development of depression or depres-

Table 2. Depression status in reserpine users and non-reserpine users.

	Reserpine user ($n = 787$)	Non-reserpine user ($n = 787$)	<i>P</i> -value
Zung depression score	40.4 ± 10.8	40.6 ± 10.7	0.70
Depression classification			
No	689 (87.6%)	694 (88.2%)	0.86
Mild	74 (9.4%)	67 (8.5%)	0.56
Moderate	19 (2.4%)	25 (3.2%)	0.34
Severe	5 (0.6%)	1 (0.1%)	0.12

Data are presented as means ± SD or n (%).

Table 3. Depression status in patients 80 years or older.

	Reserpine user ($n = 102$)	Non-reserpine user ($n = 84$)	<i>P</i> -value
Zung depression score	40.0 ± 12.3	41.5 ± 11.0	0.399
Depression classification			
No	87 (85.3%)	70 (83.3%)	0.89
Mild	9 (8.8%)	9 (10.7%)	0.46
Moderate	4 (3.9%)	5 (6.0%)	0.54
Severe	2 (2.0%)	0	0.34

Data are presented as means ± SD or n (%).

sive symptoms, the use of reserpine as anti-hypertension drug should be discouraged. On the contrary, because reserpine is a very effective antihypertensive agent, especially when used as part of a 2- or 3-drug regimen and has outcomes data attesting to its effectiveness,^[4-7,8,16] and compared to other classes of anti-hypertensive medications, reserpine is relatively cheap and has a very long duration of action (days) and may therefore be helpful to enhance patient adherence, then the role of reserpine as an antihypertensive agent should be reconsidered, particularly in economically developing countries and areas such as China.

4.1 Limitations

The major limitation of our study is the nature of cross-sectional design. Another important limitation of our study is that we used a self-rating scale to assess depression status which may overestimate or underestimate depression prevalence in hypertensive patients.^[26] However, the prevalence of depression and the mean depressive score in our studied subjects are comparable to those results of most studies on the prevalence of depression in patients with hypertension.^[27]

4.2 Conclusions

In conclusion, our present study shows that there is no association between low-dose reserpine use and depression in older hypertensive patient. This result, combined with other recent studies on the safety and tolerability of low dose reserpine as an anti-hypertension medication, strongly suggest that the role of reserpine in the treatment and control of hypertension should be reconsidered, and further studies, especially randomized, controlled clinical trials to compare efficacy and safety of reserpine and other widely recommended anti-hypertensive agents are needed.

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