Clinical Study on the Effect of 851R oral liquid Delaying Senility

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The clinical study on the effect of 851 R delaying senility was principally based on the relevant provisions of *the Screening Regulation and Clinical Observation Standard on Herbal Medicine Delaying Senility,* which was drawn up at the third national meeting of gerontology association.

Materials and Methods

Ⅰ **Case screening: Meet the requirements:** (1) Age: Aged persons 60~69 years old; Pre-Aged persons 50~59 years old. (2) Focus on the patients having deficiency syndromes of kidney and spleen. (3) Patients with severe diseases of heart, lung, liver, kidney, brain and endocrine system were excluded.

Ⅱ **Clinical grouping and treating methods**

Randomized controlled trials were adopted: cases of different gender and similar Traditional Chinese Medicine diagnosis were allocated to two groups at random under the condition that the average age difference was within 5 years. 851R oral liquid was given 50ml t.i.d. in the treatment group (hereinafter referred to as group A), Good-for-Youth oral liquid was given 10ml b.i.d in the control group(hereinafter referred to as group B), and the period was three months for both. There were 73 cases in group A and 70 cases in group B. there were 128 cases in group C, which is for observation on extended clinical therapy. The information about gender and age in the three groups was listed on table 1 and table 2. There was no significant difference (P>0.1), according to statistical analysis, in the three groups.

Table 1. The average age of each group

Group	Case	Age($\bar{x} \pm s$)
A	73	58.63±5.37
B	70	58.84±6.38
C	128	59.15±5.19

Table 2. The gender distribution of each group

Group	Male	Female	Total
A	35	38	73
B	33	37	70
C	70	58	128

Ⅲ Criterion of Traditional Chinese Medicine Categorical Identification and Therapeutic Effect Assessment

1. Criterion of Traditional Chinese Medicine Categorical Identification
   Score and make a definitive Traditional Chinese Medicine diagnosis in accordance with appendix 1 Criterion of Assessing Senility in All Deficiency Syndromes of Kidney and Spleen:
   (1) all deficiency syndromes of kidney must have 2 main symptoms, 3 minor symptoms and 1 symptom from inspection or palpation, or the score is no less than 13.
   (2) All deficiency syndromes of spleen must have 2 main symptoms, 2 minor symptoms and 1 symptom from inspection or palpation, or the score is no less than 12.
   (3) 1 or more than 1 symptom from inspection or palpation gets 6, and 0 for none.
   (4) For minor symptoms, obvious symptom or symptom occurring continuously gets 3, symptom occurring at interval or in varying degrees gets 2, and mild or occasional symptom gets 1. For main symptoms, the score doubles after assessing by the criterion on degree.
2. Criterion of Therapeutic Effect Assessment
   (1) Conspicuous: the score decreases by ≥2/3
   (2) Effective: the score decreases by ≥1/3, but not reaching ≥2/3.
   (3) Inert: the score decreases by ＜1/3

Ⅳ Modern Science Objective indictors Testing

(1) Routine blood test, routine urine test, glycosuria, blood urea nitrogen(BUN), and alanine aminotransferase (ALT).
(2) Cardiogram
(3) Antioxidation Capacity: CuZn superoxide dismutase (Cu-ZN-SOD), Mn superoxide dismutase (Mn-SOD), lipid peroxidation (LPO), glutathione (GSH) and glutathione peroxidase (GSH-PX), urine hydroxyproline.
(4) Blood T Lymphocyte : CD_3(total T lymphocytes), CD_4 (helper T lymphocytes) and CD_8 (suppressor T lymphocytes)
(5) Testosterone (T), estradiol(E_2), T/E_2
(6) Pulmonary function tests: vital capacity (VC), forced vital capacity（FVC）, forced expiratory volume in the first second（FEV_1%）and maximal voluntary ventilation (MVV)
(7) Brain function: Verbal Fluency and Word Memory

Ⅴ Observation Method

Before therapy, the complete case history should be recorded, and wholesome and the overall modern science objective checkup be conducted. During therapy, clinical observation should be performed once a week. After therapy, a full re-checkup is required to assessing the therapeutic effect.

Ⅵ Statistical analysis

Paired T test is used for measurement material within group to make comparison between that before therapy and that after therapy. T test is used for measurement material between groups.
Radit analysis is used for rank material.

Results

Ⅰ Clinical therapeutic effect:

See table 3.Through Ridit analysis, the therapeutic effect of Qi-deficiency of kidney in Group A and that in Group C were both higher than that in group B (P<0.05). $\overline{R}$ of the rest symptoms in Group A was higher than that in group B, but there was no significant difference because the cases were not enough. The conspicuous rate and effective rate of the total therapeutic effect on deficiency of kidney and spleen were calculated, and they were45.2% and 98.6% in Group A(73case), 5.7% and 58.6% in group B(70case), and 44.5% and 95.3% in Group C(128case). Through Ridit analysis, the therapeutic effect in Group A and in Group C were both higher than that in Group B (P<0.01).
Table 4. was the analysis of score variation of deficiency syndrome of spleen and kidney. The score of Group A and that of Group B are similar before therapy, but the degree of score declining in Group A was higher than that in Group B after therapy. The score variation of Group C was similar to that of Group A.

Table 3. The therapeutic effect analysis table of deficiency syndrome of spleen and kidney

Deficiency type	Group	Case	Marked effect	Effect	No effect	$\overline{R}$
Renal Qi deficiency	A	39	15	23	1	0.6418**
	B	42	2	24	16	0.3683
	C	64	24	38	2	0.6358**
Renal Yang deficiency	A	8	7	1	0	0.6426**
	B	5	1	4	0	0.3157
	C	19	11	7	1	0.4885
Renal Yin deficiency	A	11	5	6	0	0.6653**
	B	11	1	4	6	0.3347
	C	25	11	12	2	0.6309**
Spleen Qi deficiency	A	9	2	7	0	0.5278**
	B	8	0	3	5	0.2226
	C	15	8	6	1	0.6313**
Spleen Yang deficiency	A	5	4	1	0	0.5667
	B	1	0	1	0	0.1667
	C	0	0	0	0	

Spleen Yin deficiency	A	1	0	1	0	0.4444
	B	3	0	1	2	0.2222
	C	5	3	2	0	0.6778*
Total	A	73	33	39	1	
	B	70	4	37	29	
	C	128	57	65	6	

Table 4. Analysis table on score variation of deficiency syndrome of spleen and kidney

Deficiency type	Group	Case	Pretreatment	Post-treatment	Changes before and after
Renal Qi deficiency	A	39	21.5±4.7	9.4±3.5	(-)12.1±3.5△△**
	B	42	21.9±4.9	13.2±3.4	(-)8.7±4.8△△
	C	65	21.3±4.9	9.2±4.0	(-)12.1±5.1△△
Renal Yang deficiency	A	11	17.8±3.4	6.5±8.7	(-)11.3±2.4△△**
	B	11	18.5±3.6	12.5±3.2	(-)6.0±3.0△△
	C	23	20.3±5.9	10.6±3.7	(-)9.7±6.4△△
Renal Yin deficiency	A	8	19.4±4.6	6.1±2.4	(-)13.3±4.0△△
	B	5	20.8±5.4	12.4±4.9	(-)8.4±4.3△△
	C	20	21.7±7.2	7.5±4.3	(-)14.2±7.6△△
Spleen Qi deficiency	A	9	18.8±4.0	8.0±2.1	(-)10.8±2.9ΔΔ
	B	8	20.0±3.4	13.6±2.1	(-)6.2±2.9ΔΔ
	C	13	18.8±6.9	8.3±2.8	(-)10.5±7.1ΔΔ
Spleen Yang deficiency	A	1			
	B	3	18.3±2.1	10.7±3.3	(-)7.6±4.7△△
	C	5	17.8±5.6	7.4±3.3	(-)10.4±8.4ΔΔ
Spleen Yin deficiency	A	5	17.8±3.8	6.0±3.4	(-)11.8±1.1ΔΔ
	B	1			
	C	0			

Note: ①In the Changes before and after, (+) Represents an increase and (-) Indicates decrease.

②Δ represents comparison with pretreatment;

* represents comparison with B group.

Same in late table.

Variation of Anti-oxidation Capacity:

See table 5. GSH were increased remarkably in all the three groups after therapy.

GSH-PX were increased remarkably in all the three groups after therapy.

LPO in all the three groups decreased remarkably therapy.

Mn-SOD increased remarkably in all the three groups after therapy.

Cu-Zn-SOD were increased remarkably in groups A, groups B after therapy

TAA were increased remarkably only in groups C after therapy, increased not remarkably in group A, which may result from the high level before therapy

Table 5. Analysis on change of Anti-oxidation Capacity

Item	Group	Case	Pretreatment	Post-treatment	Changes before and after
GSH (mg/gHb)	A	67	2.430±0.459	3.242±0.760	(+)0.812±0.772△△
	B	67	2.453±0.331	3.129±0.478	(+)0.676±0.483△△
	C	128	2.382±0.575	3.192±0.668	(+)0.810±0.696△△
GSH-PX (μ/gHb)	A	67	678.2±203.5	780.9±115.4	(+)102.7±195.3△△
	B	67	590.7±159.8	814.3±125.4	(+)223.6±192.2△△
	C	113	678.1±170.7	843.3±150.1	(+)166.2±222.5△
LPO (μmol/ml)	A	67	5.477±1.435	4.126±0.805	(-)1.351±1.475△△
	B	67	5.460±1.780	4.110±0.860	(-)1.350±1.940△△
	C	127	5.650±2.173	4.259±0.901	(-)1.381±2.250△△
Mn-SOD (Nu/ml)	A	67	48.07±10.72	61.21±5.997	(+)13.14±2.197△△
	B	67	45.42±10.51	59.25±7.300	(+)13.83±12.80△△
	C	127	49.29±9.920	53.89±11.19	(+)4.50±18.37△△
Cu-Zn-SOD (u/gHb)	A	66	1162±163.0	1344±81.81	(+)182±187.0△△
	B	67	1158±173.9	1293±120.8	(+)135±236.3△△
	C	127	1289±787.8	1355±882.4	(+)66±1173
Total antioxidative activity	A	68	30.47±4.328	31.31±3.408	(+)0.84±4.470
	B	66	28.80±4.720	30.71±3.160	(+)1.91±4.520
	C	127	28.18±4.910	30.68±3.449	(+)2.50±5.402△

Variation of urine hydroxyproline:

See table 6. The values increased remarkably in group B and group C after therapy, increased not remarkably in group A, which may be high level before therapy.

Table 6. Analysis on change of urine hydroxyproline Unit : μmol/mmol.Cr

Group	Case	Pretreatment	Post-treatment	Changes before and after
A	67	8.847±5.227	8.2211±6.6952	(-)0.546±6.226
B	65	6.200±4.360	9.180±4.84	(+)2.980±4.450
C	125	5.313±3.899	8.630±5.039	(+)3.317±4.196△△

Variation of sex hormone:

See table 7.

(1) Male: Testosterone in all the three groups after therapy showed increasing not remarkably; E_2 only in Group B increased remarkably after therapy. T/E_2 in all the three groups decreased remarkably after therapy

(2) Female: E_2 in Group A decreased remarkably after therapy. T in groups A decreased remarkably after therapy, and T/E_2 did not change remarkably in all the three groups.

Table 7 Analysis on change of sex hormone

Item	Group	Case	Pretreatment	Post-treatment	Changes before and after
T	A	31	18.63±5.862	19.28±5.637	(+)0.65±4.530
（Male）	B	32	20.55±6.180	22.20±6.670	(+)1.65±6.59
（nmol/L）	C	67	20.68±7.660	19.43±7.750	(-)1.25±7.987
T	A	36	1.313±0.6363	1.065±0.5244	(-)0.248±0.6568△
（Female）	B	34	0.8870±0.4590	0.9510±0.6568	(+)0.064±0.6370
（nmol/L）	C	53	0.9693±0.4707	1.089±0.7387	(+)0.120±0.8425
E2	A	31	0.5046±0.0321	0.1177±0.1802	(+)0.0672±0.1850
（Male）	B	32	0.0476±0.0205	0.0790±0.032	(+)0.032±0.0295△△
（nmol/L）	C	68	0.0649±0.0399	0.0769±0.0528	(-)0.0056±0.1075
E2	A	36	0.0254±0.0396	0.0528±0.0934	(+)0.0274±0.7612△△
（Female）	B	34	0.0615±0.1561	0.1034±0.3043	(+)0.0418±0.2222
（nmol/L）	C	55	0.1697±0.6570	0.0984±0.2564	(-)0.0456±0.1975
T/E2	A	30	419.7±236.0	259.6±123.7	(-)210.5±229.4△△
（Male）	B	32	449.5±206.9	323.5±140.3	(-)126.0±223.9△△
	C	58	398.8±193.8	321.1±151.8	(-)77.7±185.4△△
T/E2	A	36	107.2±78.68	66.99±106.0	(-)37.21±137.3
（Female）	B	33	68.50±45.70	66.8±45.80	(-)1.7±57.50
	C	48	81.93±43.56	71.71±46.35	(-)10.22±45.44

Change of T Lymphocyte:

See table 8. CD_3 increased remarkably in all the three groups after therapy,

CD_4 increased remarkably in all the three groups after therapy

CD_8 increased remarkably only in Group A after therapy, not change remarkably in Group C, which may be the high level before therapy.

CD_4/CD_8 increased remarkably only in Group C.

Table 8 Analysis on change of immunity indicators

	Group	Case	Pretreatment	Post-treatment	Changes before and after
CD_3 %	A	67	56.82±10.49	65.61±9.236	(+)8.79±10.87△△
	B	66	59.00±10.40	67.60±8.400	(+)8.60±12.20△△
	C	120	55.22±14.55	63.28±12.11	(+)8.06±16.83△△
CD_4 %	A	67	39.06±7.228	45.46±7.846	(+)6.40±9.306△△
	B	66	39.17±9.000	45.60±6.800	(+)6.43±10.79△△
	C	121	38.50±8.545	43.93±9.548	(+)5.43±10.70△△
CD_8 %	A	67	27.36±8.056	31.43±6.589	(+)4.07±8.093△△
	B	66	28.41±7.030	30.98±6.463	(+)2.57±10.382
	C	120	29.18±7.974	29.19±8.337	(+)0.01±11.67
CD_4/CD_8	A	67	1.550±0.569	1.494±0.351	(-)0.056±0.606
	B	66	1.441±0.413	1.531±0.361	(+)0.091±0.570
	C	119	1.401±0.410	1.526±0.430	(-)0.125±0.603△

Change of pulmonary function:

See table 9. VC, FVC and MVV increased remarkably in all the three groups after therapy. FEV_1 increased remarkably in group A.

Table 9 Analysis on change of pulmonary volume and pulmonary ventilation

	Group	Case	Pretreatment	Post-treatment	Changes before and after
VC %	A	29	0.6924±0.2171	0.8420±0.1925	(+)0.1496±0.1217△△
	B	25	0.6715±0.1487	0.8276±0.1007	(+)0.1561±0.1533△△
	C	42	1.0192±0.1576	1.0570±0.1688	(+)0.0380±0.0735△△
FVC %	A	29	0.6694±0.2167	0.8165±0.1915	(+)0.1471±0.1314△△
	B	26	0.6424±0.1520	0.7795±0.1192	(+)0.1370±0.1679△△
	C	42	1.0192±0.1576	1.0570±0.1688	(+)0.0380±0.0735△△
FEV_1 %	A	29	0.8917±0.0882	0.8081±0.0951	(-)0.0843±0.1380△
	B	26	0.8543±0.1379	0.8272±0.1015	(-)0.0271±0.1265
	C	42	0.7163±0.1234	0.7372±0.1258	(+)0.0209±0.0829
MVV %	A	29	0.7080±0.1904	0.8429±0.1786	(+)0.1216±0.1353△△
	B	26	0.6630±0.1522	0.7963±0.1807	(+)0.1233±0.1841△△
	C	42	0.9588±0.2389	1.0164±0.2468	(+)±0.0527±0.1358△

Variation of Brain Function:

See table 10. & 11.

(1) Change of word memory: Including point to memory, associated learning, image free recall, recognition meaningless graphics, associated remember of portrait character, memory quotient (MQ). The treatment group achieved better improvement than the control group at associative learning, recollecting characteristic of portrait and memory quotient.

Table 10 Analysis on change of word memory Units： min.

Group	Case	Point to memory	Associated learning	Image free recall	Recognition meaningless graphics	Associated remember of portrait character	MQ
A	40	-3.60±4.98	-5.23±4.59	-0.72±5.62	0.78±4.68	-2.93±5.23	-9.95±6.64
B	40	-3.55±4.06	-1.90±5.65	-1.48±5.65	0.83±4.86	0.28±4.61	-6.63±6.68
P		>0.05	<0.01	>0.05	>0.05	<0.01	<0.05

(2) Change of verbal fluency: Including speaking similar word, speaking dissimilar words, reading black words, reading color, reading color words, reading word color, writing fluency. The treatment group achieved better improvement than the control group at speaking different word, reading color, writing fluency.

Table 11 Analysis on change of verbal fluency Units：Sec.

Group	Case	Speaking similar word	Speaking dissimilar words	Reading black words	Reading color	Reading color words	Reading word color	Writing fluency
A	40	0.69±1.21	1.83±4.67	0.61±4.40	4.03±6.94	1.22±10.22	5.69±9.26	14.67±35.39
B	40	0.24±1.54	-0.46±3.46	-0.05±4.71	0.98±7.36	-0.62±7.26	-0.77±16.36	1.91±5.76
P		>0.05	<0.05	>0.05	>0.05	>0.05	<0.05	<0.05

Observation on relevant side effects

(1) ALT: there was no increase seen in Group A and in Group C, while there was increase seen in 1 cases of Group B.

(2) Proteinuria, glycosuria showed no obvious variation after therapy. BUN showed normal after review

(3) No new abnormality occurred in cardiogram of the three groups

(4) No new abnormality appeared in routine blood test of the three groups

(5) Part case reflects the unpleasant taste and bad taste when oral, with no adverse reactions in clinical.

Typical Cases

Sample1 A Chen was male, 60 years old, and had completed junior college course. He was hospitalized for high blood pressure for 2 years. He was diagnosed as hypertension I phase. The TRADITIONAL CHINESE MEDICINE categorical identification was Qi-deficiency of Kidney. He felt fine after therapy. The symptoms of headache, dizziness, weakness in lower limbs were improved. He could sleep well and eat well. Thick black hair grew on his temples. The total score reduced from 30 to 9. It was a conspicuous case. The blood pressure declined from 22/13Kpa to 20/12Kpa. In the test of brain function, MQ had risen from 69 to 90, gaining 21, after therapy. Out of 7 items of word fluency, 5 improved, and the total response time had reduced to 138.71m from 191.83m, reducing 53.12m.

Sample2 A Wang was female, 50 years old, and graduated from vocational secondary school. The chief complain was the sensation of fullness in the upper abdomen for 12 years. The diagnosis was chronic gastritis. The TRADITIONAL CHINESE MEDICINE categorical identification was Qi-deficiency of spleen. The symptoms were eased after therapy, especially her appetite and sleeping. The total score reduced from 18 to 6, a conspicuous case too. In the test of brain function, MQ had risen from 123 to 140, gaining 17, after therapy. Out of 7 items of word fluency, 6 improved, and the total response time had reduced to 137.79m from 168.43m, reducing 30.64m.

Sample3 A Lin was female, aged 50 (past 49). She had been asthenia for a long time, with aversion to cold, cold extremities, sensation of heaviness in the head as if it had been wrapped, tiredness and inertia, poor appetite and sleeping, diarrhea or constipation, which mentioned as the above turned severer when she was exhausted for her overwork, emotionally turbulent, or in seasonal fluctuation. The TRADITIONAL CHINESE MEDICINE categorical identification was Yang-deficiency of kidney and spleen. She had been taking 851R oral liquid for 3 months from July this year. All symptoms were greatly relieved, especially for tiredness and inertia. She used to feel the shortness of breath when going up stairs. Now it was gone. Her strength enhanced greatly, and she was in royal spirits. She can eat and sleep as normal or even beyond, with free movement of the bowels. The sensation of heaviness in the head disappeared. She underwent menstruation again in September, which had been suspended for 2 years, and no irregular menstruation and side effects occurred up to now. The laboratory examination: GSH rose from 2.54mg/gHb to 3.29mg/gHb, GSH-PX from 637.3u/gHb to 773.9u/gHb. Mn-SOD and Cu-Zn-SOD rose from 55.38u/ml and 1274.4u/gHb to 62.25u/ml and 1400.5u/gHb separately. The total anti-oxidation ability increased from 31.1% to 35.1%. the value of T lymphocyte sub-group returned to normal from below (CD_3 45 CD_4 31 CD_8 18 before therapy; CD_3 67 CD_4 41 CD_8 25 after therapy).

Discussion and Summary

Ⅰ The randomized controlled trials in clinical study were planned so reasonably that many aspects were comparable between treatment group and control group; therefore the conclusion drawn upon them was reliable. The therapeutic effect of the extended clinical therapy group was basically the same with that of the treatment group, which indicated that the therapeutic effect was stable. The variation of objective indicators in extended clinical treatment group (Group C) was basically the same with treatment group (Group A), which could be used as supplement.

Ⅱ As for Traditional Chinese Medicine clinical therapeutic effect. 851R oral liquid was better than Good-for-Youth oral liquid. The scores of deficiency syndrome of kidney and spleen declined remarkably in both groups, but they decreased by a larger margin for 851R oral liquid. It inferred that both the two liquids possessed capacity of tonifying kidney and spleen, but 851R oral liquid had a stronger effect. Of all the cases of deficiency syndrome of kidney most are cases of Qi-deficiency syndrome of kidney, and some are cases of Yin-deficiency or Yan-deficiency syndrome of kidney. It may be taken for granted that the main role of 851R oral liquid is to replenish kidney essence, and due to the principle that Yin and Yang are mutually funded, it also has some effect for Qi-deficiency, Yin-deficiency, and Yang-deficiency of kidney. When it comes to deficiency syndrome of spleen, Qi-deficiency of spleen is more common, and Yin-deficiency and Yan-deficiency are both rare. The role of invigorating spleen and enriching Qi may be without doubt, but the effect for Yin or Yan of spleen is left for further study. Therefore, as far as TRADITIONAL CHINESE MEDICINE clinical pharmacology is concerned, the role of 851R oral liquid may be summed up as replenishing kidney essence, invigorating spleen and enriching Qi.

Ⅲ Based on the variation of modern science objective indicators, the roles of 851R oral liquid were concluded as the following

(1) Develop anti-oxidation capacity and clear free radical. Raise the content of GSH, GSH-PX, Cu-Zn-SOD, Mn-SOD. Boost up serum total anti-oxidation activity. Reduce the content of LPO in blood . These are comprehensive and outstanding, promoting normal, correcting abnormal.
(2) Reinforce the synthesis and degradation of collagen.
(3) For female, it raises the level of E_2, reduce the content of T in blood and returns the T/E_2 ratio which is too high before therapy to normal.
(4) Raise the level of CD_3(total T lymphocytes), CD_4 (helper T lymphocytes) and CD_8 (suppressor T lymphocytes)
(5) Improve respiratory function: increase VC, FVC and MVV.
(6) Improve brain function, including speaking dissimilar words, reading word color, writing fluency of verbal fluency and associated learning, associated remember of portrait character, memory quotient (MQ) of word memory.

The effects of Good-for-Youth are similar to that of 851R oral liquid in many

aspects, though its effect of increasing antioxidation capacity is not very obvious. For male Good-for-Youth raises the level of testosterone and returns the T/E_2 ratio to normal, 851R oral liquid is not very obvious.

Ⅳ According to the TRADITIONAL CHINESE MEDICINE theory that spleen is the origin of the acquired constitution and kidney is the origin of congenital constitution, senility is closely related to deficiency of kidney and spleen. 851R oral liquid can replenish kidney essence, tonify spleen and enrich Qi, so it can naturally delay senility. 851R oral liquid has the effects of anti-oxidation, clearing off free radical, increasing collagen metabolic process, improving internal environment of sex hormone, improving cell immunity and enhancing the function of lung and brain on multi-aspects. On the ground of modern medical theory about senility, there are many to interpret senility, such free radical theory, crosslinking theory, decreased sex hormone function theory, immunity theory, and organ degeneration theory and so on. No matter what theory, it can explain the therapeutic effect of 851R oral liquid delaying senility.

Ⅴ The therapeutic effect of 851R oral liquid delaying senility is definite. It is safe for delaying senility and no adverse reactions.