The observation on curative effect of Shouhuitongbian capsule in the treatment of functional constipation: A real world study

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Research

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Abstract

Background: Chronic constipation is a common disease caused by a variety of reasons. This study was to observe the improvements on symptoms, quality of life and satisfaction of patients with functional constipation by Shouhuitongbian capsule, and evaluate its safety.

Methods: The study was divided into four groups according to the duration of disease. The primary observational indicators were efficacy and safety of Shouhuitongbian capsule after 14 days of treatment, and changes of Wexner score of intestinal function. Effect of Shouhuitongbian capsule on quality of life of patients, and the long-term efficacy and safety of taking capsule after 1 month, 2 months and 3 months were used as secondary observational indicators .

Results: The results showed that the improvement effect of capsules on 14th day was better than on the 7th day ($P=0.001$). Besides, compared with patients with longer duration of disease, the improvement effect of patients with shorter duration of disease was better ($P=0.001$). The long-term improvement effect of patients taking capsules was greater than the short-term improvement effect ($P=0.001$). The long-term improvement of patients with shorter duration of disease after taking capsules was more effective than that of patients with longer duration of disease ($P=0.001$).

Conclusion: The experimental results provide a strong/powerful/ convincing evidence for the re-evaluation of efficacy and safety of Shouhuitongbian capsule after its marketing.

Introduction

Chronic constipation is a common disease caused by a variety of reasons, among which constipation caused by abnormal colorectal and anal functions is called functional constipation [1, 2]. It is clinically regarded as an independent disease, characterized by fecal frequency reduction, difficulty in defecation, inexhaustible defecation, dry and hard stool, and barium or enteroscopy without organic lesions [3]. At present, the prevalence of functional constipation is about 2% – 27% [4]. With the change of lifestyle and the aging of population, the prevalence of functional constipation is increasing, which seriously affects people's quality of life. Constipation can not only cause hemorrhoids, anal fissure and other anal diseases, but also induce and aggravate various cardiovascular and cerebrovascular diseases, and even cause colon cancer, endangering life [5, 6].

Functional constipation can be divided into three types according to its location and the characteristics of colonic dynamics: slow transit constipation (STC), outlet obstruction constipation (OOC), and mixed constipation (MC) [7]. STC is a constipation caused by colonic motility disorder, which results in slow discharge of intestinal contents or retention in the colon. OOC is an anorectal dysfunction caused by non-organic factors, but its intestinal dynamics and function are normal. MC is a kind of constipation with both of the above characteristics. However, the etiology and pathogenesis of chronic functional constipation have not been fully understood in modern medicine [8]. So far, there are no effective, long-term and less side effects drugs for functional constipation. In most cases, patients mainly rely on

laxatives to make their stools smooth [9]. Although the short-term effect of laxatives is fine, long-term use can produce tolerance, and may cause serious bowel diseases such as "cathartic colon" and "melanosis coli". Afterwards, it will make the condition of constipation worse and complex, which is difficult to recover over time. Some patients may also take surgical treatment due to unsatisfactory efficacy of drugs, which may damage physical function of patients.

Traditional Chinese medicine (TCM) has a unique theoretical basis and accumulated thousands of years of clinical experience. It has been based on the principle of individualized treatment and makes different treatment plans for patients according to different characteristics. Therefore, it shows certain advantages in the treatment of functional constipation. Although there are many TCM on the market for constipation at present, clinical multi-center non-intervention experimental studies are scarce. The prescription of Shouhuitongbian capsule comes from a long-term clinical practice. It is composed of Polygonum multiflorum, Aloe vera, Cassia seed, Donkey hide gelatin, Chinese wolfberry, Ginseng, Atractylodes macrocephala and Bitter orange. The clinical practice proves that it exhibited quick, definite curative, and no-toxic effects, especially for functional constipation. To demonstrate the efficacy and safety of capsule, we conducted a multi-center, prospective, non-interventional real-world clinical trial from May 2018 to June 2019.

Materials And Methods:

Subjects

This is a multi-center, prospective and non-interventional real world study conducted in 30 centers. The aim was to describe efficacy of Shouhuitongbian capsule in treating more than 2396 patients with functional constipation for 14 consecutive days within 4 months. The project was approved by the relevant ethics committee. Before treatment, all participants received detailed information about the study and voluntarily joined with informed consents.

The exclusion criteria of the study were: patients with constipation caused by organic lesions; patients with secondary constipation of clear etiology; patients who had used functional constipation drugs in the past two weeks; patients with abnormal liver function (ALT, AST > 3ULN); pregnant or pregnant women, lactating women; allergic constitution or allergic to this medicine. Inclusion criteria were as follows: voluntary participation; age 18-80 years; meeting Rome III diagnostic criteria for functional constipation [10]; conforming to syndrome diagnostic criteria for deficiency of both Qi and Yin combined with toxic pathogens; patients taking Shouhuitongbian capsule for at least one course of treatment.

Methods

This is a non-interventional study, so Shouhuitongbian capsule should be given to the subjects separately before deciding to include them in the study. The prescribing of Shouhuitongbian capsule for a course (14 days) would be conducted in accordance with routine clinical practice at the hospital concerned. All

procedures performed in these visits conformed to routine clinical practice. The Shouhuitongbian capsule was provided by Lunan Houpu Pharmaceutical Co., Ltd. with packing specification of 0.35g x 6 capsules. All centers strictly screened out qualified patients, and only one treatment period (7 days) of drugs is given to each visit. Drug administrators should fill in the "Record Form of Drug Delivery in Clinical Trials" in time. It is forbidden to add any other Chinese and Western medicines that have a similar effect to the tested drugs during the test period.

Effectiveness Assessments

The main therapeutic index of this study was the change of Wexner score of intestinal function before and after treatment. The items were defecation frequency, difficulty degree (pain assessment), integrity (incomplete sensory assessment), abdominal pain, time spent in toilet, assistant form and failure number (failure number of attempted defecation in 24 hours). The above items were given 0-30 points according to different performance. The lower score, the lighter condition, accordingly, the higher score, the more serious disease. The observation indexes were observed and recorded before and on the eighth and fifteenth days after the experiment.

The secondary treatment indicator was quality of life scale (PAC-QOL) for constipation patients. PAC-QOL has been developed into the Chinese version, with 28 items in total, involving patients' physiology, social psychology, anxiety, satisfaction and other aspects. The 5-point Likert method is used for alternative answers. Degree was divided into five levels, such as none, a little, general, more serious and very serious. So did frequency, for example, none, occasionally, sometimes, often and always. The corresponding scores of 5-point Likert method for each item were 0, 1, 2, 3 and 4, respectively. At the same time, the long-term effect of Shouhuitongbian capsule on functional constipation was observed after taking it for 1 month, 2 months and 3 months.

Adverse events and adverse reactions

Various adverse events and adverse reactions were closely observed, and occurrence time, degree of manifestation, treatment process and results were recorded in detail. Pay attention to whether there are serious adverse events and adverse reactions. The causal relationship between adverse events and experimental drugs was assessed according to the 5-level criteria as affirmative, probable, possible, probably not relevant and irrelevant supplied by Adverse Drug Reaction Monitoring Center of the Ministry of Health.

Data analysis

SPSS19.0 was used for statistical analysis. The differences of relevant indicators and TCM syndrome integral before and after the intervention of Shouhuitongbian capsule of the study population were compared by the student t test. The chi-square test was used for counting data. $P < 0.05$ was considered statistically significant.

Results

Demographic Characteristics

A total of 2396 cases were included in this study, of which 47% were males and 53% were females. Average age was 50.6 ± 14.9 years, average height was 166.1 ± 7.3 cm, average weight was 64.0 ± 11.3 kg, average BMI was 23.1 ± 3.3 kg/m², and average duration of disease was 38.8 ± 104.3 months. Among them, the number of patients with 0-6 months and 1-5 years of illness was the largest, accounting for 32.4% and 37.4% of the total number, respectively. The patients of 7-12 months and more than 5 years accounted for 15.9% and 14.3%, respectively. The average Wexner score before admission was 12.4 ± 4.8 . 23.7% of patients had received western medicine treatment, while only 16.5% had received TCM treatment (Figure 1).

TCM syndromes of patients with different duration of constipation

According to duration of constipation, patients were divided into four groups. Table 1 shows that most patients defecate twice a week, among which patients with duration of more than five years were up to the highest proportion ($P=0.001$). The longer disease course, the lower proportion of defecation 1-2 times per 1-2 days. Most patients sometimes or often have difficulty in defecating. Among them, the longer disease duration, the higher proportion of patients who often have difficulty in defecating ($P=0.001$). Most patients spent 10-20 minutes in toilet, and the proportion of patients who spent more than 30 minutes in toilet increased with the prolongation of disease duration ($P=0.001$). The proportion of patients requiring assisted defecation increases with the disease duration ($P=0.001$). Only 24.4% of patients with duration of 0-6 months need irritant laxatives, while 44.7% of patients with a duration of more than 5 years need it.

Wexner score in patients with different duration of constipation

Wexner score of four groups were shown in Table 2. The results of inter-group comparisons showed that Wexner score of patients increased with prolongation of disease duration. The patients with a disease duration of more than 5 years obtained higher score than other groups ($P=0.001$). The results of intra-group comparison showed that Wexner score decreased with the increase of medication duration. Wexner score of each group after 14 days of treatment were significantly lower than those before and 7 days after treatment ($P=0.001$). Patients whose duration of disease is more than 5 years occupied the lowest rate of clinical recovery (only 27.5%), but nearly 49.4% of patients'symptoms were significantly improved, which held the highest rate.

TCM symptom therapeutic effect score in patients with different duration of constipation

The TCM symptom therapeutic effect score of four groups was shown in Table 3. The results of inter-group comparisons showed that the patients with a disease duration of 1-5 years gained higher scores than other groups before treatment and after medication 7 days ($P=0.001$). On the 14th day of medication, patients with a duration of more than 5 years possessed the highest TCM symptom

therapeutic effect score. The results of intra-group comparisons showed that TCM symptom therapeutic effect score decreased with the increase of medication duration ($P=0.001$). The clinical rehabilitation rate of patients with a course of more than 5 years was the lowest (29.1%) and improved symptoms among them were the highest (34.2%).

Quality of life of patients with different duration of constipation

The quality of life score of four groups was shown in Table 4. The results of inter-group comparisons showed that the patients with a disease duration of 1~5 years achieved higher scores than other groups before treatment ($P=0.001$). On the 2nd, 8th, 10th and 12th weekend of treatment, patients with duration of more than 5 years exhibited the highest quality of life score ($P=0.05$). However, the results of intra-group comparison implied that quality of life score decreased with the increase of treatment time ($P=0.001$).

Patient satisfaction rating with different duration of constipation

Patient satisfaction rating of four groups was shown in Table 5. The results of inter-group comparisons indicated that satisfaction rating of patients increased with the course of disease. The patients with a disease course of more than 5 years were significantly higher than in other groups ($P=0.001$). While the results of intra-group comparison suggested that satisfaction rating decreased with the increase of treatment time ($P=0.001$).

Safety evaluation

The safety assessment results were shown in Table 6. 81.2% of the patients were considered that the safety level of this study was level 1, and adverse events did not occur among 99% of the patients. Therefore, Shouhuitongbian capsule has no adverse effect on the safety in this study.

Discussion

Due to acceleration of life rhythm and change of dietary habits, and heavy working pressure, more and more people are likely to suffer from chronic constipation, which has attracted extensive attention of the medical community. Dry stool, difficulty or discomfort in defecation, fecal frequency reduction are common clinical symptoms of constipation. At present, the etiology of functional constipation is not completely clear. However, intestinal neuropathy, smooth muscle degeneration, central neuropathy and abnormal gastrointestinal hormones are relative to the etiology [11].

According to TCM, direct cause of constipation is malfunction of large intestine conduction, which is based on deficiency and excess [12]. The pathogenesis of patients with excessive large intestinal conduction function is mostly pathogenic stagnation of gastrointestinal tract and obstruction, which can be divided into intestines and stomach heating, stagnation of Qi and stagnation of cold. The pathogenesis of patients with insufficient large intestinal conduction function is mostly intestinal dryness and poor motility, including Qi deficiency, blood deficiency, Yin deficiency and Yang deficiency. Although

there are many causes of functional constipation, the main clinical manifestations are deficiency and heat. The treatment is usually combined deficiency and excess.

The Shouhuitongbian capsule used in this study consists of Polygonum multiflorum, Aloe vera, Cassia seed, Donkey hide gelatin, Chinese wolfberry, Ginseng, Atractylodes macrocephala and Bitter orange. Modern pharmacological studies have shown that the active ingredient in Polygonum multiflorum is anthraquinone compound, which can promote intestinal movement and exhibit distinct cathartic effect [13]. Aloin, an active ingredient in aloe, could be converted into aloe emodin through hydrolysis and oxidation, and promote intestinal peristalsis [14]. Cassia seed played a significant role in lowering blood pressure, blood lipid and moistening intestine, and its curative effect is mild and lasting [15]. Donkey hide gelatin possesses the effect of nourishing blood, yin and moistening dryness [16]. Chinese wolfberry displayed the function of nourishing liver, kidney and lungs. It is a good medicine for the treatment of intestinal dryness and constipation [17]. Atractylodes macrocephala can promote the secretion of gastrointestinal tract, and peristalsis is increased [18]. Except for promoting intestinal peristalsis, bitter orange could also relax intestinal smooth muscle. The advantages of Shouhuitongbian capsule is that combining Polygonum multiflorum and Aloe vera, which strengthens the functions of clearing heat, detoxifying, moistening intestines and purging bowels.

Dietary fiber and Western medicine are usually used as the treatment of constipation. However, it is reported that colonic transit time can't be shortened by increasing intestinal water content, and dietary fiber may lead to abdominal distension and stool hardening [19]. Western medicine treatment of constipation revealed some defects such as great side effects and poor tolerance, and there was still no progress at present. Therefore, the treatment of constipation with TCM has become a research hotspot at this stage. This study compared the efficacy of Shouhuitongbian capsule in treating four groups of functional constipation patients with different duration of disease through a large sample of real world study. The results showed that Shouhuitongbian capsule could significantly improve the frequency, nature and difficulty of defecation of all patients, and the improvement effect was gradually enhanced with the prolongation of the duration of treatment. However, compared with patients with a longer duration of disease, patients with a shorter duration of disease exhibited better defecation effect ($p \leq 0.001$). By comparing the changes of life quality and satisfaction of the four groups, it was found that with the prolongation of medication time, the quality of life and satisfaction of all patients were improved. The improvement of life quality and satisfaction of patients with shorter duration of disease was significantly higher than those with longer duration of disease ($p \leq 0.01$). In view of the above results, doctors can increase or decrease the time and frequency of medication according to the different duration of patients.

Conclusions

Shouhuitongbian capsule showed a good effect on improving the symptoms of functional constipation patients in each group, but it has a better effect on patients with shorter duration of disease. No obvious side effects and adverse reactions were found in clinical trials. The results provide strong evidence for re-

evaluation of efficacy and safety of Shouhuitongbian capsule after its marketing. The limitation of this study is that it only compares the effect, quality of life and satisfaction of Shouhuitongbian capsule on functional constipation of patients with different duration of disease, but fails to study its mechanism and pharmacology and toxicology. It will be the focus of future research.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Competing interests

All authors declare that they have no competing interests.

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Contributions

Hongxi Zhang, and Bao Han designed the research. Zhiyun Zhang, and Yongduo Yu performed the experiments. Hongxi Zhang, and Bao Han provided the resources. Zhenguo Tian wrote the original draft. Yongduo Yu and Hongxi Zhang review and editing the paper. All authors read and approved the final manuscript.

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Tables

Table 1. TCM symptom of different duration of constipation.

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Frequency of defecation n(%)					
1-2 times per 1-2 days	194 (25.0 %)	68 (17.8 %)	103 (11.5 %)	43 (12.6 %)	<0.001
Twice a week	310 (39.9 %)	160 (42.0 %)	376 (41.9 %)	157 (45.9 %)	
Once a week	164 (21.1 %)	91 (23.9 %)	265 (29.5 %)	94 (27.5 %)	
Less than once a week	106 (13.7 %)	59 (15.5 %)	147 (16.4 %)	46 (13.5 %)	
Less than once a month	2 (0.3 %)	3 (0.8 %)	6 (0.7 %)	2 (0.6 %)	
Difficulty: Pain assessment n(%)					
never	81 (10.4 %)	36 (9.4 %)	47 (5.2 %)	36 (10.5 %)	<0.001
Very seldom	216 (27.8 %)	93 (24.4 %)	186 (20.7 %)	64 (18.7 %)	
sometimes	262 (33.8 %)	138 (36.2 %)	316 (35.2 %)	121 (35.4 %)	
Often	169 (21.8 %)	84 (22.0 %)	280 (31.2 %)	94 (27.5 %)	
always	48 (6.2 %)	30 (7.9 %)	68 (7.6 %)	27 (7.9 %)	
Integrity: Incomplete sensory Assessment n(%)					
never	73 (9.4 %)	30 (7.9 %)	47 (5.2 %)	21 (6.1 %)	<0.001
Very seldom	221 (28.5 %)	76 (19.9 %)	170 (19.0 %)	49 (14.3 %)	
sometimes	240 (30.9 %)	148 (38.8 %)	290 (32.3 %)	133 (38.9 %)	
Often	192 (24.7 %)	97 (25.5 %)	321 (35.8 %)	104 (30.4 %)	
always	50 (6.4 %)	30 (7.9 %)	69 (7.7 %)	35 (10.2 %)	
Pain: abdominal pain n(%)					

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
never	109 (14.0 %)	59 (15.5 %)	96 (10.7 %)	52 (15.2 %)	0.0845
Very seldom	254 (32.7 %)	121 (31.8 %)	240 (26.8 %)	103 (30.1 %)	
sometimes	268 (34.5 %)	131 (34.4 %)	331 (36.9 %)	119 (34.8 %)	
Often	118 (15.2 %)	53 (13.9 %)	201 (22.4 %)	53 (15.5 %)	
always	27 (3.5 %)	17 (4.5 %)	29 (3.2 %)	15 (4.4 %)	
Time: Time in the toilet (minutes) n(%)					
Less than 5	34 (4.4 %)	9 (2.4 %)	11 (1.2 %)	7 (2.0 %)	<0.001
5-10	184 (23.7 %)	82 (21.5 %)	181 (20.2 %)	61 (17.8 %)	
10-20	308 (39.7 %)	177 (46.5 %)	374 (41.7 %)	144 (42.1 %)	
20-30	176 (22.7 %)	81 (21.3 %)	234 (26.1 %)	88 (25.7 %)	
More than30	74 (9.5 %)	32 (8.4 %)	97 (10.8 %)	42 (12.3 %)	
Auxiliary: Auxiliary Form n(%)					
No	486 (62.6 %)	238 (62.5 %)	455 (50.7 %)	113 (33.0 %)	<0.001
Irritant laxatives	189 (24.4 %)	103 (27.0 %)	300 (33.4 %)	153 (44.7 %)	
Finger assistance or enema	101 (13.0 %)	40 (10.5 %)	142 (15.8 %)	76 (22.2 %)	
Failure: Number of failed attempts to defecate 24 hours n(%)					
No	130 (16.8 %)	74 (19.4 %)	121 (13.5 %)	45 (13.2 %)	0.001
1-3 times	418 (53.9 %)	219 (57.5 %)	497 (55.4 %)	189 (55.3 %)	
3-6 times	161 (20.7 %)	56 (14.7 %)	228 (25.4 %)	84 (24.6 %)	

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
6-9 times	58 (7.5 %)	27 (7.1 %)	39 (4.3 %)	16 (4.7 %)	
More than 9 times	9 (1.2 %)	5 (1.3 %)	12 (1.3 %)	8 (2.3 %)	

Table 2. Wexner constipation score of patients

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Before medication n(%)					
n(nmiss)	776(0)	381(0)	897(0)	342(0)	
Mean±SD	11.3± 5.2	11.7± 4.9	13.0± 4.2	14.3± 4.0	<0.001
7th day of medication n(%)					
n(nmiss)	776(0)	381(0)	897(0)	342(0)	
Mean±SD	6.5± 4.1	6.7± 3.9	7.3± 3.7	8.3± 4.1	<0.001
Intra-group comparison between pre-medication and 7th days of medication n(%)					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
14th day of medication n(%)					
n(nmiss)	776(0)	381(0)	897(0)	342(0)	
Mean±SD	3.8± 3.2	3.6± 2.9	4.1± 2.9	5.9± 3.6	<0.001
Intra-group comparison between pre-medication and 14th days of medication n(%)					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
Therapeutic criteria (Wexner constipation score system) n(%)					
Clinical recovery: clinical symptoms basically disappeared, symptom score decreased by more than 90%.	399 (51.4 %)	190 (49.9 %)	404 (45.0 %)	94 (27.5 %)	<0.001
Significant effect: The clinical symptoms were significantly improved, and the symptom score was reduced by more than 70%.	274 (35.3 %)	141 (37.0 %)	359 (40.0 %)	169 (49.4 %)	
Effective: Clinical symptoms improved, symptom score decreased by more than 30%.	98 (12.6 %)	48 (12.6 %)	123 (13.7 %)	73 (21.3 %)	

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Invalid: clinical symptoms did not improve significantly, or even worsen, symptoms score decreased by less than 30%.	5 (0.6 %)	2 (0.5 %)	11 (1.2 %)	6 (1.8 %)	

Table 3. TCM symptom therapeutic effect score in patients

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Before medication n(%)					
n(nmiss)	776(0)	381(0)	897(0)	342(0)	
Mean±SD	4.5± 2.4	4.7± 2.4	5.2± 2.4	5.1± 2.2	<0.001
7th day of medication n(%)					
n(nmiss)	776(0)	381(0)	897(0)	342(0)	
Mean±SD	2.6± 1.8	2.6± 1.8	3.0± 2.0	2.9± 2.0	<0.001
Intra-group comparison between pre-medication and 7th days of medication n(%)					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
14th day of medication n(%)					
n(nmiss)	776(0)	381(0)	897(0)	342(0)	
Mean±SD	1.4± 1.4	1.2± 1.4	1.5± 1.6	1.8± 1.8	<0.001
Intra-group comparison between pre-medication and 14th days of medication n(%)					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
Evaluation of curative effect of TCM syndromes integral n(%)					
Clinical recovery: clinical symptoms basically disappeared, symptom score decreased by more than 90%.	260 (34.7 %)	160 (43.1 %)	316 (35.9 %)	97 (29.1 %)	0.4079
Significant effect: The clinical symptoms were significantly improved, and the symptom score was reduced by more than 70%.	158 (21.1 %)	66 (17.8 %)	198 (22.5 %)	67 (20.1 %)	
Effective: Clinical symptoms improved, symptom score decreased by more than 30%.	224 (29.9 %)	100 (27.0 %)	273 (31.1 %)	114 (34.2 %)	
Invalid: clinical symptoms did not improve significantly, or even worsen, symptoms score decreased by less than 30%.	107 (14.3 %)	45 (12.1 %)	92 (10.5 %)	55 (16.5 %)	

Table 4. Quality of life of patients

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Before treatment					
n(nmiss)	601(175)	306(75)	727(170)	261(81)	
Mean±SD	43.7± 22.7	46.5± 23.6	49.5± 20.2	46.9± 20.9	<0.001
2nd weekend of treatment					
n(nmiss)	569(207)	282(99)	633(264)	236(106)	
Mean±SD	13.2± 14.3	11.3± 13.1	15.1± 13.7	18.7± 14.5	<0.001
Intra-group comparison between before treatment and 2nd weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
4th weekend of treatment					
n(nmiss)	167(609)	88(293)	231(666)	103(239)	
Mean±SD	12.7± 13.4	10.9± 12.8	13.3± 14.9	15.3± 11.9	0.1529
Intra-group comparison between before treatment and 4th weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
6th weekend of treatment					
n(nmiss)	122(654)	69(312)	188(709)	65(277)	
Mean±SD	11.6± 12.4	8.9± 11.8	13.1± 14.5	13.5± 11.9	0.1078
Intra-group comparison between before treatment and 6th weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
8th weekend of treatment					
n(nmiss)	140(636)	77(304)	212(685)	80(262)	
Mean±SD	10.6± 11.2	7.9± 11.0	11.1± 12.7	13.8± 11.9	0.0216

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Intra-group comparison between before treatment and 8th weekend of treatment					
	<i>p</i> = <0.001	<i>p</i> = <0.001	<i>p</i> = <0.001	<i>p</i> = <0.001	
10th weekend of treatment					
n(nmiss)	118(658)	64(317)	182(715)	65(277)	
Mean±SD	10.0± 11.6	5.4± 8.1	10.6± 11.8	12.8± 10.1	0.0013
Intra-group comparison between before treatment and 10th weekend of treatment					
	<i>p</i> = <0.001	<i>p</i> = <0.001	<i>p</i> = <0.001	<i>p</i> = <0.001	
12th weekend of treatment					
n(nmiss)	206(570)	116(265)	328(569)	125(217)	
Mean±SD	8.4± 10.6	6.5± 8.7	10.6± 11.6	12.8± 10.7	<0.001
Intra-group comparison between before treatment and 12th weekend of treatment					
	<i>p</i> = <0.001	<i>p</i> = <0.001	<i>p</i> = <0.001	<i>p</i> = <0.001	

Table 5. Patient satisfaction rating

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Before treatment					
n(nmiss)	601(175)	306(75)	727(170)	261(81)	
Mean±SD	10.6± 4.0	11.0± 3.7	11.4± 3.5	12.0± 3.3	<0.001
2nd weekend of treatment					
n(nmiss)	569(207)	282(99)	633(264)	236(106)	
Mean±SD	3.1± 2.8	2.7± 2.7	3.5± 2.8	4.7± 3.1	<0.001
Intra-group comparison between before treatment and 2nd weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
4th weekend of treatment					
n(nmiss)	167(609)	88(293)	231(666)	103(239)	
Mean±SD	3.0± 2.7	3.0± 3.0	3.5± 3.0	4.7± 2.8	<0.001
Intra-group comparison between before treatment and 4th weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
6th weekend of treatment					
n(nmiss)	122(654)	69(312)	188(709)	65(277)	
Mean±SD	2.4± 2.4	2.2± 2.6	3.1± 2.9	4.3± 2.8	<0.001
Intra-group comparison between before treatment and 6th weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
8th weekend of treatment					
n(nmiss)	140(636)	77(304)	212(685)	80(262)	

	0-6 months (N=776)	7-12 months (N=381)	1-5 years (N=897)	More than 5 years (N=342)	<i>p</i>
Mean±SD	2.5± 2.3	2.2± 2.5	3.1± 2.9	4.1± 3.0	<0.001
Intra-group comparison between before treatment and 8th weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
10th weekend of treatment					
n(nmiss)	118(658)	64(317)	182(715)	65(277)	
Mean±SD	2.3± 2.3	2.0± 2.5	3.0± 2.6	4.4± 2.7	<0.001
Intra-group comparison between before treatment and 10th weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	
12th weekend of treatment					
n(nmiss)	206(570)	116(265)	328(569)	125(217)	
Mean±SD	1.9± 2.1	1.8± 2.3	2.7± 2.5	3.9± 2.8	<0.001
Intra-group comparison between before treatment and 12th weekend of treatment					
	p= <0.001	p= <0.001	p= <0.001	p= <0.001	

Table 6. Safety assessment

	Subjects (N=2396)
Safety level of this study	
Level 1	1946 (81.2 %)
Level 2	435 (18.2 %)
Level 3	13 (0.5 %)
Level 4	2 (0.1 %)
Are there any adverse events?	
Yes	24 (1.0 %)
No	2372 (99.0 %)

Figures

Figure 1

Demographic characteristics of subjects