

Clinical Study on the Treatment of Pediatric Primary Nocturnal Enuresis by Integrated Traditional Chinese and Western Medicine

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To investigate the curative effect of integrated traditional Chinese and Western medicine in the treatment of children with primary nocturnal enuresis is the objective of the study. 160 children with primary nocturnal enuresis were randomly divided into four groups and received suoquan capsules, solifenacin combined with suoquan capsules, solifenacin or behavioral intervention for 2 mo. The response rates of each group were evaluated and logistic regression analysis was used to analyze the influencing factors of curative effect. In addition, the patients were followed up after 3 mo to investigate the recurrence rate. The complete remission (complete response) rate in solifenacin combined with suoquan capsules group was higher than that in behavioral intervention group (37.5 % vs. 7.5 %, $p=0.007$). The complete response rate and non-response rate in the solifenacin group were lower than those in the solifenacin combined with suoquan capsules group (all $p<0.05$). The recurrence rate in the solifenacin group was significantly higher than that in the solifenacin combined with suoquan capsules group (72.5 % vs. 30.0 %, $p=0.027$). Multivariate analysis showed that treatment group, enuresis frequency and age were independent predictors of complete response at 2 mo. Integrative traditional Chinese and Western medicine has good effect in the treatment of children with primary nocturnal enuresis and the recurrence rate is low. Enuresis frequency, treatment method and age were important predictors of complete remission after treatment.

Key words: Solifenacin, nocturnal enuresis, recurrence rate, suoquan capsules

Pediatric Primary Nocturnal Enuresis (PNE) is a common disease in children over 5 y old, as children cannot urinate on their own. Most of the symptoms are difficult to wake up, unconscious urination in sleep and no abnormality in the urinary system^[1]. According to relevant data^[2], about 5 % to 19 % of children with Nocturnal Enuresis (NE) are PNE, which has a serious impact on the physical and mental health of children, and requires great attention. At present, there is no unified clinical method for the treatment of PNE and drug treatment is mostly used for the disease. Suoquan capsules is composed of radix *Linderae*, *Alpinia oxyphylla* and yam, which can help to reduce bladder detrusor excitability and urine concentration^[3], but single medication has problems such as high Recurrence Rate (RR) and slow curative effect. As a new generation of M-receptor blockers, solifenacin is commonly used in the treatment of overactive bladder. Studies have shown that, the application of low-dose

solifenacin in pediatric PNE can effectively improve the curative effect and reduce recurrence^[4]. At present, there have been some reports on the therapeutic effect of low-dose solifenacin in PNE^[5], but there are few reports on the therapeutic effect of solifenacin combined with suoquan capsules in children with PNE and further research is needed. This study attempts to explore its application effect and value through grouped controlled trials, which are reported as follows.

MATERIALS AND METHODS

Subjects:

160 children with PNE who were prospectively enrolled in the Department of Pediatrics of Guangdong Maternal and Child Health Hospital from January 2019 to December 2020 were selected as the research objects and were divided into group A (suoquan capsules) and group B by random number table method,

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(solifenacin combined with suoquan capsules), group C (solifenacin) and group D (behavioral intervention). There were 40 children in each group and all children met the following inclusion and exclusion criteria.

Inclusion criteria: Those who meet the diagnostic criteria of PNE; those who were 5 to 14 y old; those who have NE frequency ≥ 3 times/w and last for >3 mo; no patients with severe cardiopulmonary disease; patients with normal urine test; family members of the children voluntarily signed the informed consent for this study.

Exclusion criteria: Those who received treatment of 3 mo before admission; patients with clinical insufficiency of important organs such as liver and kidney; patients with blood system diseases; patients with local infection or systemic infection; with immunodeficiency; with diabetes, spina bifida, urinary system and other diseases; with mental illness; allergic to therapeutic drugs; those with poor compliance; those who were naturally lost to follow-up.

Treatment methods:

Group A: Oral suoquan capsules (Hansen Pharmaceutical, Yiyang, Hunan, China), 3 tablets each time (0.3 g/tablet), 3 times a day.

Group B: On the basis of oral shrinkage gel treatment, additional solifenacin tablets (Guoyao Zhunzi H20183365, Sichuan Guowei Pharmaceutical Co., Ltd., specification: 5 mg/tablet), 2/3 tablets each time, once a day.

Group C: Take 2/3 solifenacin tablets orally each time, once a day.

Group D: Children in group D require changes in unhealthy lifestyle and bladder and wake up training. Wake up training means wake the child to urinate before enuresis which may occur, according to the bedwetting time rule; or wake the child to urinate when the child turns suddenly during quiet sleep. Bladder training means train the children to urinate regularly and in correct urination posture; try to increase bladder capacity by encouraging children to drink plenty of water and to delay urination for extended periods of time during the day, twice a day; teach children to interrupt urine flow to strengthen pelvic muscles.

Evaluation index:

After 2 mo of treatment in each group, the number and percentage of non-responders, partial responders and complete responders were assessed. No Response (NR) was defined as a decrease of 0 %-49 %. A Partial

Response (PR) was defined as 50 %-99 % reduction. Complete Response (CR) is defined as a 100 % reduction. Relapse was defined as the recurrence of symptoms more than 1 time per month.

Statistical analysis:

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 19.0. Continuous variables in each group were expressed as mean \pm standard deviation and were compared using t test. Categorical variables were expressed as rates or percentages, chi-square tests were used for comparison and logistic regression models were used to analyze factors affecting complete remission, $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

From January 2019 to December 2020, a total of 236 children were diagnosed with PNE in our hospital of which 42 patients were excluded from this study: 19 patients did not meet the inclusion criteria; 15 patients did not provide informed consent; 8 patients did not participate in the follow-up and finally 160 children were included in the study. Among them, 92 were male and 68 were female, with an average age of 8.1 ± 1.7 y (5-14 y). There were no statistically significant differences in baseline clinical characteristics among the four groups and were comparable (Table 1).

Remission and relapse rates in the study were explained here. The CR (37.5 %) of the solifenacin combined with suoquan capsules group was higher than that of the behavioral intervention group (7.5 %, $p = 0.008$). The CR (22.5 %) of solifenacin group was lower than that of solifenacin combined with suoquan capsules group (CR, 37.5 %, $p = 0.016$). There was no significant difference in CR between the suoquan capsules group and the solifenacin combined with suoquan capsules group. The RR of the solifenacin group was significantly higher than that of the solifenacin combined with suoquan capsules group ($p = 0.009$) (Table 2).

The impact of demographic characteristics on the CR rate is as follows. Children in each group were stratified according to gender, age, family history of NE, frequency of NE, maternal education level and presence of urgent symptoms, and CR was compared among patients at different levels. The CR of children with urgency symptoms treated with solifenacin combined with suoquan capsules was higher than that in solifenacin group ($p = 0.002$) and behavioral intervention group ($p = 0.001$) (Table 3).

TABLE 1: COMPARISON OF SUBJECTS BASELINE CHARACTERISTICS

Variables	Suoquan capsules (n, %)	Solifenacin		Behavioral intervention (n, %)	P
		combined with suoquan capsules (n, %)	Solifenacin (n, %)		
Gender					
Male	22 (55.0)	23 (57.5)	24 (60.0)	23 (57.5)	0.883
Female	18 (45.0)	17 (42.5)	16 (40.0)	17 (42.5)	
Age					
5-10 y	25 (62.5)	26 (65.0)	21 (52.5)	23 (57.5)	0.266
11-15 y	15 (38.5)	14 (35.0)	19 (47.5)	17 (42.5)	
Family history					
None	27 (67.5)	27 (67.5)	19 (47.5)	23 (57.5)	0.218
Present	13 (32.5)	13 (32.5)	21 (52.5)	17 (42.5)	
Mother's education level					
Below middle school	19 (47.5)	19 (47.5)	14 (35.0)	16 (40.0)	0.767
Middle school	12 (30.0)	13 (32.5)	22 (55.0)	19 (47.5)	
University and above	9 (22.5)	8 (20.0)	4 (10.0)	5 (12.5)	
Urgency					
Present	16 (40.0)	17 (42.5)	29 (72.5)	25 (62.5)	0.248
None	24 (60.0)	23 (57.5)	11 (27.5)	15 (37.5)	
NE frequency (times/week)					
2-4	1 (2.5)	3 (7.5)	6 (15.0)	5 (12.5)	0.624
5-7	32 (80.0)	29 (72.5)	19 (47.5)	19 (47.5)	
≥8	7 (17.5)	8 (20.0)	15 (37.5)	16 (40.0)	

TABLE 2: COMPARISON OF THE TREATMENT OUTCOMES OF THE FOUR GROUPS OF CHILDREN

Group	CR, n (%)	PR, n (%)	NR, n (%)	RR, n (%)
Suoquan capsules	8 (20.0)	20 (50.0)	12 (30.0)	17 (42.5)
Solifenacin combined with suoquan capsules	15 (37.5)	16 (40.0)	9 (22.5)	12 (30.0)
Solifenacin	9 (22.5)	21 (52.5)	10 (25.0)	29 (72.5)
Behavioral intervention	3 (7.5)	23 (57.5)	14 (35.0)	1 (2.5)

TABLE 3: IMPACT OF DEMOGRAPHIC CHARACTERISTICS ON CR RATES

Variables		CR rate			
		Suoquan capsules (n, %)	Solifenacin combined with suoquan capsules (n, %)	Solifenacin (n, %)	Behavioral intervention (n, %)
Gender	Male	4 (18.2)	8 (34.8)	6 (25.0)*	3 (13.0)*
	Female	4 (22.2)	7 (41.2)	3 (18.8)*	0 (0.0)*
Age	5-10 y	6 (24.0)*	12 (46.2)*	6 (28.6)	1 (4.3)
	11-15 y	2 (13.3)*	3 (21.4)*	3 (15.8)	2 (11.8)
Family history	None	5 (18.5)	9 (33.3)	6 (31.6)	2 (8.7)
	Present	3 (23.1)	6 (46.2)	3 (14.3)	1 (5.9)
Mother's education level	Below middle school	4 (21.1)	8 (42.1)	3 (21.4)	1 (6.3)**
	Middle school	3 (25.0)	4 (30.8)	4 (18.2)	1 (5.3)**
	University and above	1 (11.1)	3 (37.5)	2 (50.0)	1 (20.0)**
Urgency	None	4 (16.7)	7 (41.2)	5 (17.2)	2 (8.0)
	Present	4 (25.0)	8 (34.8)	4 (36.4)	1 (6.7)
NE frequency (Number of times/ week)	2-4	1 (100.0)**	0 (0.07)	1 (16.7)**	1 (20.0)**
	5-7	4 (12.5)**	13 (44.8)	8 (42.1)**	2 (10.5)**
	≥8	3 (42.9)**	2 (25.0)	0 (0.0)**	0 (0.0)**

Note: *p<0.05 and **p<0.01

Influencing factors of CR rate were explained here. Patients were stratified according to age, sex, family history of NE, frequency of NE, treatment group, urgency and maternal education level, and CR rates were compared between groups. The results showed that treatment mode, frequency of NE and age was associated with treatment effect (Table 4).

Multivariate indicators of CR rate are shown here. Logistic regression models were used to analyze successful responses and predictions with 3 important factors in group comparisons (treatment method, age and frequency of NE) as independent variables and response rate as dependent variable (CR, 0; PR and NR, 1) and relationship between variables (Table 5). NE frequency, treatment method and age were independent predictors of successful treatment response at 2 mo.

NE can be divided into primary NE and secondary NE. PNE refers to enuresis since childhood, no bed-wetting period of more than 6 mo and organic diseases are excluded, while secondary enuresis refers to the recurrence of bed-wetting period after a previous period of 6 mo or more^[6]. This study mainly discusses PNE. Solifenacin is a new-generation M3 receptor subtype antagonist with 6.5 times the affinity for M3 in smooth muscle compared to the M3 receptor on salivary glands, with fewer adverse reactions and better tolerability. In addition, solifenacin half-life is as long as 45-68 h and it can be administered once a day. Solifenacin can also reduce the frequency of

urgency, incontinence, urination and nocturia in patients, and increase the average single voiding volume, which is related to the safety of the drug. The incidence of adverse reactions was significantly reduced^[7,8]. Suoquan capsules is a traditional Chinese medicine commonly used to treat NE in children, which helps to reduce bladder detrusor excitability and urine concentration, but this traditional Chinese medicine is not common worldwide.

Fujinaga *et al.* showed that solifenacin produced a statistically significant reduction in the number of wet nights (62.9 %) compared to placebo (2.4 %)^[9]. The success rate of solifenacin for the treatment of NE varies from 10 % to 65 %. The CR rate of solifenacin in this study (30.0 %) was consistent with that of Ghanavati *et al.*^[4], but lower than that of Fujinaga *et al.*^[9]. This difference may be related to short-term medication, efficacy standards and ethnic or sociocultural differences. This study compared the efficacy of four different therapies in children with NE after 2 mo. The CR rate of solifenacin combined with suoquan capsules group (37.5 %) was higher than that of behavioral intervention group (6.3 %, $p < 0.007$), suggesting that the combined treatment of NE is more effective than behavioral intervention. The RR in the solifenacin group was significantly higher than that in the solifenacin combined with suoquan capsules group ($p < 0.007$), which indicated that NE was easy to recur when solifenacin alone was treated and this result was consistent with previous studies^[10].

TABLE 4: FACTORS AFFECTING CR IN CHILDREN WITH NE

Parameters	Variables	n	CR (n, %)	χ^2	p
Gender	Male	92	21 (22.8)	1.878	0.232
	Female	68	14 (20.6)		
Age	5-10 y	95	25 (26.3)	4.323	0.029
	11-15 y	65	10 (15.4)		
Family history	None	96	22 (22.9)	0.446	0.258
	Present	64	13 (20.3)		
	Solifenacin	40	9 (22.5)		
Treatment method	Solifenacin combined with suoquan capsules	40	15 (37.5)	28.133	0.000
	Suoquan capsules	40	8 (20.0)		
	Behavioral intervention	40	3 (7.5)		
Mother's education level	Below middle school	68	16 (23.5)	0.924	0.066
	Middle school	66	12 (18.2)		
	University and above	26	7 (26.9)		
Urgency	None	87	18 (20.7)	0.366	0.578
	Present	73	17 (23.3)		
NE frequency (number of times/week)	2-4	15	3 (20.0)	14.988	0.001
	5-7	99	27 (27.3)		
	≥ 8	46	5 (10.9)		

Note: χ^2 : Chi-squared test

TABLE 5: MULTIVARIATE ANALYSIS OF THE THERAPEUTIC EFFECT OF NE

Factors	β	Standard Error (SE)	Wald	p	OR	95 % CI	
						Lower limit	Upper limit
NE frequency	0.787	0.232	9.587	0.001	2.123	1.246	3.398
Treatment method	-0.268	0.121	4.278	0.027	0.776	0.588	0.947
Age	0.583	0.269	4.580	0.016	1.826	1.121	3.231

Note: β : Beta coefficient; OR: Odds Ratio and CI: Confidence Interval

Water vapor protein 2 (Aquaporin 2, AQP-2) is the only water vapor protein regulated by Antidiuretic Hormone (ADH) (also known as Arginine Vasopressin (AVP)), AQP-2 can regulate human water balance through water reabsorption and urine concentration. Cao *et al.* showed that suoquan capsules can increase the expression of AQP-2 messenger Ribonucleic Acid (mRNA) and Arginine Vasopressin Receptor 2 (AVPR-V2) mRNA, thereby concentrating urine^[3]. Li *et al.*^[11] studies have shown that suoquan capsules can directly stimulate the secretion of aldosterone to reduce urine output. Tan *et al.*^[12] showed that suoquan capsules enhanced the sensitivity of beta (β)-Adrenergic Receptor (β -AR), which mediates detrusor relaxation, but reduced the purine nucleotide X receptor. Sensitivity to nucleotide X receptors dominates detrusor contractions. Furthermore, β_3 -AR, a subtype of β -AR, mediates detrusor relaxation and antagonizes M receptors. Xu *et al.*^[13] found that suoquan capsules could increase the sensitivity and expression of β_3 -AR in aging rats. Previous studies have shown that suoquan capsules can not only reduce urine volume and concentrate urine, but also reduce the excitability of bladder detrusor. From the perspective of traditional Chinese medicine, an important cause of enuresis is long-term deficiency of kidney yang. Suoquan capsules have a good effect on invigorating the kidney and strengthening yang, so it also has a certain effect on enuresis. These are also the reasons why the RR of the suoquan capsules combined with solifenacin is lower than that of the solifenacin alone treatment group. The RR of solifenacin group was higher than that of suoquan capsules group, but the difference was not statistically significant.

The incidence and duration of NE in males exceeds than that in females. Hofmeester *et al.* have shown that gender (female) is a predictor of the success of adaptive dry bed training in adolescent NE patients^[14], the results of which are inconsistent with the results of this study. In this study, the CR rate of male children in solifenacin group and behavioral intervention group was higher than that of female children. This difference may be related to the different samples of participants in this study. In addition, the female children progressed to sexual

maturity earlier. Tai *et al.*^[15] showed that older children were more affected by family and psychological problems than younger children. Therefore, female children may be more susceptible to unhealthy psychological factors. In addition, treatment was an independent factor for CR (Odds Ratio (OR), 0.781; 95% Confidence Interval (CI): 0.618-0.987). The CR rate of solifenacin combined with suoquan capsules group was higher than that of behavioral intervention group.

This study has certain limitations. Due to poor compliance in some families, this study did not compare the urine output before and after treatment during the day and night. During the course of treatment, this study did not adjust the dose of solifenacin in time, nor did it gradually reduce the dose during the follow-up; therefore, the RR rate was higher in the solifenacin group. In conclusion, this study shows that integrated traditional Chinese and Western medicine is safe and effective in the treatment of NE in children and is worthy of widespread clinical use.

Conflict of interests:

The authors declared no conflict of interest.

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