

## The Treatment of Nocturnal Enuresis in Children: An Overview

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### Abstract

**Background:** The aim of this review was to compare the efficacy of acupuncture therapy in the treatment of nocturnal enuresis with placebo acupuncture or oral pharmacological treatment based on randomized controlled trials.

**Materials and Methods:** Two independent researchers screened the meta-analysis articles on the effect of treatment nocturnal enuresis in children. The databases included Scopus, EMBASE, Cochrane, Web of Science, and Medline, with no time and language restrictions from the beginning up to March 10, 2020.

**Results:** The first meta-analysis showed that therapy with the combination of desmopressin and anticholinergics (combination therapy) was significantly better than desmopressin monotherapy. The second meta-analysis showed that structured withdrawal from desmopressin treatment compared with the abrupt withdrawal results in a significantly better relapse-free rate (pooled RR: 1.38; 95% confidence interval [CI]: 1.17–1.63; P=0.0001). The third meta-analysis reported a 31% rate of successful treatment for rapid palatal expansion, which is promising compared to the spontaneous cure rate. In the fourth meta-analysis, the pooled data showed a significant difference between acupuncture and meclofenoxate therapy (OR=2.81). No significant difference was observed between acupuncture, desmopressin (OR = 1.57), imipramine hydrochloride (OR = 1.71), and oxybutynin (OR = 3.57). In the fifth meta-analysis, a statistically significant difference was observed between the frequency of enuresis per week (P < 0.001), the number of patients with clinical response (P < 0.001), and bladder capacity (P < 0.001) in the electrical stimulation (ES) group compared with the placebo group.

**Conclusion:** Therapy with the combination of desmopressin and anticholinergics (combination therapy) produced significantly better results than desmopressin monotherapy. The findings showed the positive effects of acupuncture therapy and rapid palatal expansion on nocturnal enuresis in children.

**Key Words:** Children, Nocturnal enuresis, Treatment, Overview.

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## 1- INTRODUCTION

Urinary incontinence is one of the most common problems in children. It is defined as the loss of bladder control in children older than five years, which cannot be attributed to any specific cause or drug use (1). Nocturnal enuresis has two types: primary enuresis, when the child has never before attained bladder control for six consecutive months; and secondary enuresis, when the incontinence recurs in the child after six months of continuous urinary continence (2). Urinary incontinence can be the manifestation of several problems, including stress, psychological responses, and social isolation, and slow maturation, feelings of worthlessness, incompetence, and low self-esteem. Parents' indifference, ignorant reactions, contemptuous behavior of family and peers, and sometimes even bodily punishment are common and will exacerbate the problem and delay the treatment (3).

The treatment for urinary incontinence are non-pharmacologic and pharmacologic. Non-pharmacologic treatments include motivational therapy (MT), behavioral therapy, and bladder continence training. Pharmacologic treatments involve imipramine, anticholinergics, and desmopressin (4). The prevalence of nocturnal enuresis in five-year-old boys and girls is 7% and 0.3%, respectively. The prevalence in 10-year-old boys and girls is 3% and 2%, respectively (5). The etiology of nocturnal enuresis is not well understood. Possible causes include developmental problems in the central cortex, irregularities in the circadian antidiuretic hormone (ADH) secretion leading to increased nighttime urine production, rapid eye movement (REM) sleep behavior disorder, and musculoskeletal tension reduction (5). The etiology of primary nocturnal enuresis is generally linked to the bladder developmental and functional issues, and

that of secondary enuresis to the stressogenic life experiences. Cultural differences in child nurturing are also essential factors in different rates of nocturnal enuresis (6). Unfortunately, there are few published overviews on the treatment of nocturnal enuresis in children. The aim of this paper is to compare the efficacy of acupuncture therapy in the treatment of nocturnal enuresis with placebo acupuncture or oral pharmacological treatment based on randomized controlled trials (RCTs).

## 2- MATERIALS AND METHODS

Two independent researchers screened the articles on the efficacy of treatment of nocturnal enuresis in children. The searched databases included Scopus, EMBASE, Cochrane, Web of Science, and Medline, with no time and language restrictions from the beginning up to March 10, 2020. Possible disagreements were resolved by a third member of the faculty.

## 3- RESULTS

At the end of the screening, five meta-analyses were selected for the study. The pooled effect estimates by Chua et al. showed that the efficacy of a one-month therapy with desmopressin and anticholinergics (combination therapy) resulted in a significantly better immediate response rate than desmopressin monotherapy. Subgroup analysis showed a better immediate one-month response rate among desmopressin-resistant patients than treatment-naive patients. No significant adverse effect was observed among the groups treated with combination therapy (7). Pooled effect estimates of four randomized controlled trials by Chua et al. showed that the structured desmopressin withdrawal results in a significantly better relapse-free rate (pooled RR: 1.38; 95% CI: 1.17–1.63;  $p=0.001$ ) compared with the abrupt

withdrawal. Subgroup analysis for a dose-dependent structured withdrawal regimen showed a significantly better relapse-free rate (pooled RR: 1.48; 95% CI: 1.21–1.80;  $p=0.001$ ). (8) Mir et al. assessed the effect of rapid palatal expansion on the treatment of nocturnal enuresis in children. The median treatment duration for the complete resolution of enuresis was 2.87 months (95% CI: 2.07–2.93 months). After one year, the average rate of the complete resolution was 31%. The presence of posterior cross bite (relative risk (RR): 0.31, 95% CI: 0.12–0.79), and signs of upper respiratory obstruction during sleep (RR: 5.1, 95% CI: 1.44–18.04) led to a significant decrease and increase in the chance of improvement, respectively (9) The same findings were applicable to ten other studies which compared acupuncture therapy with western medicine and showed the promising effects of acupuncture therapy on nocturnal enuresis (OR = 3.03; 95% CI: 1.88–4.88;  $p<0.01$ ). The existence of between-study heterogeneity was attested ( $I^2=56\%$ ;  $p<0.01$ ).

Pooled data indicated a significant difference between acupuncture and Meclofenoxate therapy (OR = 2.81; 95% CI: 1.62–3.96), with no sign of heterogeneity. No significant difference was found between desmopressin and acupuncture in treating NE (OR=1.57; 95% CI: 0.38–6.57). No significant difference was observed between imipramine hydrochloride and acupuncture therapy (OR = 1.71; 95% CI: 0.65–4.51). Compared with oxybutynin, acupuncture did not further improve the clinical effects (OR = 3.57; 95% CI: 0.53–2 ) (10).

Chui et al. found a statistically significant difference in the frequency of enuresis per week (mean difference [MD],  $-0.70$ ; 95% CI:  $-0.89$  to  $-0.51$ ;  $p<0.001$ ), the number of patients with clinical response (MD, 26.88; 95% CI: 11.16 to 64.74;  $p<0.001$ ), and bladder capacity (MD,  $-0.70$ ; 95% CI:  $-0.89$  to  $-0.51$ ;  $p<0.001$ ) in the electrical

stimulation (ES) group compared with the placebo group with the exception of maximum voided volume (MVV) (MD, 19.48; 95% CI:  $-9.18$  to 48.14;  $p=0.18$ ) (11).

#### 4- DISCUSSION

The aim of this review was to evaluate the efficacy of acupuncture therapy in the treatment of nocturnal enuresis compared with placebo acupuncture and oral pharmacological treatment based on RCTs. Desmopressin and anticholinergic therapy (combination therapy) had significantly better results than desmopressin monotherapy. The structured desmopressin withdrawal resulted in significantly better relapse-free rates than the abrupt withdrawal. Acupuncture therapy and rapid palatal expansion could improve nocturnal enuresis in children. Desmopressin is used in the form of nasal sprays and is absorbed quickly by nasal mucosa. The highest serum level is reached in about 45 minutes. The earliest response to the treatment appears in about two weeks after use (4). The treatment with desmopressin has shown favorable results and minor side effects. However, several studies have reported high relapse rates (7, 12, 13). The findings of a meta-analysis showed the structured desmopressin withdrawal results in significantly lower relapse rates compared with the abrupt withdrawal (8). Consequently, several retrospective studies are conducted on a structured withdrawal (time- and dose-dependent) of desmopressin therapy. The structured withdrawal was found more expensive and time-consuming; however, it achieved higher clinical success rates (8). Desmopressin monotherapy can achieve an average of 64.1% immediate response rate among monosymptomatic nocturnal enuresis patients, but resistance to desmopressin treatment is documented to be high (7, 13). Efforts are underway to develop new strategies with maximum

immediate effectiveness and minimal adverse events (7). The findings of a meta-analysis showed that combination therapy with desmopressin and an anticholinergic agent is well tolerated by treatment-naive and desmopressin-resistant pediatric enuretic patients and has a significantly better immediate one-month response rate than desmopressin monotherapy (7). Acupressure is another complementary method of treatment with 5000 years of history. The use of acupressure and similar traditional Chinese medicine can prevent imbalances in the vital energy of the body. As a result, it can lead to pain relief, reduced muscle contraction, improved blood circulation and vital bodily functions, and fewer anxiety symptoms (14). Pooled data showed a significant difference between acupuncture and meclofenoxate therapy. No significant difference was found between acupuncture and desmopressin, imipramine hydrochloride, and oxybutynin therapy (10). This study significantly advances the statistics concerning the frequency of enuresis per week, the number of patients with clinical response, and bladder capacity for children with NE compared to the placebo group with the exception of MVV (11). The treatment of urinary incontinence can either be pharmacological or non-pharmacological. Non-pharmacological treatments include motivational therapy (MT), behavioral therapy, and bladder continence training. Pharmacological treatment involves imipramine, anticholinergic agents, and desmopressin (15). Desmopressin is a synthetic analogue of arginine vasopressin which is an anti-diuretic hormone that decreases urine production. It is now recommended as the frontline drug for the treatment of nocturnal enuresis in children. The treatment with desmopressin has the average rapid response of 64.1% among the patients with monosymptomatic nocturnal enuresis. However, resistance to desmopressin treatment is high (16). The

researchers aim to develop new strategies with maximum efficiency and minimum side effects, because multimodal treatment is not generally recommended (17). Also, the results of the treatment with desmopressin are favorable and have minor side effects. The treatment with desmopressin has a rapid response, but has a high risk of recurrence in case of abrupt withdrawal. Suppressing endogenous vasopressin through vasopressin injection and its abrupt withdrawal result in a constant vasopressin deficiency. Endocrine withdrawal syndrome is a physiologic phenomenon that occurs after the withdrawal of hormonal therapy and may cause atypical hormone deficiency and generic withdrawal syndromes. Therefore, a gradual reduction in drug use is strongly recommended to prevent symptoms of the hormonal imbalance (18). Complementary and alternative medicines (CAM) are recommended to address the increasing demand for non-pharmacological treatment approaches. As one of the most popular CAM therapies, TCM-based acupressure is a common treatment option for nocturnal enuresis in traditional Chinese medicine. Compared to the conventional therapies, this method is safer, more cost-beneficial, and adaptable (19). Acupressure practices have 5000 years of history. Utilizing acupressure and the strategic points of Chinese medicine can prevent imbalances in the vital energy of the body. As a result, it can lead to pain relief, reduced muscle contraction, improved blood circulation and vital bodily functions, and fewer anxiety symptoms (14). Therapeutic acupressure is applied through perforation with thin sterile needles on particular body parts called meridian points. As an inseparable part of Traditional Chinese Medicine, acupuncture involves sophisticated theories for rearranging the five elements of fire, earth, metal, water, and wood; yin, yang, qi, blood and bodily fluids. Through the stimulation of particular points on the

body, some disorders of the organic systems may be intervened, some symptoms may be alleviated, and the internal homeostasis may be restored to normal. The acupuncture points for the treatment of nocturnal enuresis are those affecting urine centers in the spinal column and the parasympathetic urinary system. Through acupuncture stimulation, enkephalins and endogenous opioids levels will increase in the plasma and the central nervous system. After acupuncture stimulation, an increase is observed in beta-endorphin levels in the cerebrospinal fluid. Beta-endorphin per se may decrease the contractions of the urinary bladder. The clinical effects of acupuncture can be seen with suppressing spinal and supra-spinal reflexes leading to the urinary bladder contractions. The increase in the maximum capacity of the urinary bladder and suppressing detrusor overactivity reflect the clinical effectiveness of acupuncture, and these functional changes might have a role in improving nocturnal enuresis (20). Acupressure may achieve more effective clinical results in the treatment of nocturnal enuresis in children than placebo and pharmacological treatments. No major side-effect has been observed from the use of acupuncture in this context. Therefore, it can be stated that the discreet use of acupuncture may improve the clinical effects of enuresis in children (19).

#### 4-1. Study Limitations

No suitable and precise measuring and assessment tool were available for parts of the diagnoses, and variables like age, normal growth rate, intelligence quotient (IQ), and the effects of teachers' and parents' attitude will affect the evaluation results (21).

#### 5- CONCLUSION

Based on the findings of this overview, it may be suggested with discreetness that the structured

desmopressin withdrawal results in better relapse-free rates. The treatment with a combination of desmopressin and anticholinergics (combination therapy) was associated with a significantly better results than desmopressin monotherapy. Acupuncture and rapid palatal expansion therapy could improve nocturnal enuresis in children; however, the beneficial effects of acupuncture might have been overstated due to low methodological qualities. Future rigorous, high quality RCTs are needed to confirm the results.

**6- CONFLICT OF INTEREST:** None.

#### 7- REFERENCES

1. Yousefi P, Firouzifar M, Dorreh F. Growth and development in 6-year-old children with and without primary nocturnal enuresis. *J Adv Med Biomed Res.* 2012;20(82):92-8.
2. Makari JH, Rushton HG. Nocturnal enuresis in children. *Clinical evidence.* 2006(15):486-95.
3. Soleimani M, Zafarghandi S. Epidemiology of Enuresis in 7-11-Year-Old Students in Semnan. *Iranian Journal of Psychiatry and Clinical Psychology.* 2005;11(2):187-93.
4. Falak-ul-Aflaki B, Sharifi F, Torabi Z, Moezi F. Evaluation of therapeutic effect of desmopressin on enuresis in children. *J Adv Med Biomed Res.* 2007;15(58):11-6.
5. Naderian M, Ellahi H, Yarigaravesh M. Study of Nocturnal Enuresis and Adenotonsillar Hypertrophy. *Razi Journal of Medical Sciences.* 2001;7(22):331-4.
6. Dehghani K, Pourmovahed Z, dehghani h, shakiba m, Tavangar H, YASINI AS, et al. The survey of enuresis related factors in school children aged 6-12 years. 2009.
7. Chua ME, Silangcruz JMA, Chang S-J, Yang SS. Immediate 1-month efficacy of desmopressin and anticholinergic combination therapy versus desmopressin monotherapy in the treatment of pediatric enuresis: A meta-

analysis. *Journal of pediatric urology*. 2016;12(3):156. e1-. e9.

8. Chua ME, Silangcruz JM, Chang S-J, Williams K, Saunders M, Lopes RI, et al. Desmopressin withdrawal strategy for pediatric enuresis: a meta-analysis. *Pediatrics*. 2016;138(1):e20160495.

9. Mir KP-B, Mir AP-B, Mir MP-B, Moradi-Lakeh M, Balmeh P, Nosrati K. Rapid palatal expansion to treat nocturnal enuretic children: a systematic review and meta-analysis. *Journal of Dentistry*. 2015;16(3):138.

10. Lv Z-t, Song W, Wu J, Yang J, Wang T, Wu C-h, et al. Efficacy of acupuncture in children with nocturnal enuresis: a systematic review and meta-analysis of randomized controlled trials. *Evidence-Based Complementary and Alternative Medicine*. 2015;2015.

11. Cui H, Yu W, Yan H, Zhou Z, Wu J, Cui Y. The efficacy of electrical stimulation in treating children with nocturnal enuresis: A systematic review and meta-analysis. *Neurourology and Urodynamics*. 2019;38(8):2288-95.

12. Bayne AP, Skoog S. Nocturnal enuresis: an approach to assessment and treatment. *Pediatrics in review*. 2014;35(8):327-34; quiz 35.

13. Alloussi S, Mürtz G, Lang C, Madersbacher H, Strugala G, Seibold J, et al. Desmopressin treatment regimens in monosymptomatic and nonmonosymptomatic enuresis: a review from a clinical perspective. *Journal of pediatric urology*. 2011;7(1):10-20.

14. Pouraboli B, Abazari F, Rostami M, Jahani Y. Comparison the effect of two methods of acupressure and massage with ice on Huko point on pain intensity during IV

insertion in pediatrics with thalassemia. *Journal of Pediatric Nursing*. 2015;2(2):20-7.

15. Falak-ul-Aflaki B, Sharifi F, Torabi Z. Evaluation of therapeutic effect of desmopressin on enuresis in children. 2007;15(58):11-6.

16. Alloussi S, Mürtz G, Lang C, Madersbacher H, Strugala G, Seibold J, et al. Desmopressin treatment regimens in monosymptomatic and nonmonosymptomatic enuresis: a review from a clinical perspective. 2011;7(1):10-20.

17. Chua ME, Silangcruz JMA, Chang S-J, Yang SSJJopu. Immediate 1-month efficacy of desmopressin and anticholinergic combination therapy versus desmopressin monotherapy in the treatment of pediatric enuresis: A meta-analysis. 2016;12(3):156. e1-e9.

18. Chua ME, Silangcruz JM, Chang S-J, Williams K, Saunders M, Lopes RI, et al. Desmopressin withdrawal strategy for pediatric enuresis: a meta-analysis. 2016;138(1):e20160495.

19. Lv Z-t, Song W, Wu J, Yang J, Wang T, Wu C-h, et al. Efficacy of acupuncture in children with nocturnal enuresis: a systematic review and meta-analysis of randomized controlled trials. 2015;2015.

20. Zhu J, Arsovska B, Kozovska KJJoRiM, Sciences D. Nocturnal Enuresis–Treatment with Acupuncture. 2017;5(4):6-8.

21. Saeedalzakerin m, Shafyee f, Heidarnia ar, Kazemnejad a. Parents' coping strategy: drug therapy and educational techniques in the treatment of children's enuresis. *Iranian Journal of Psychiatry and Clinical Psychology*. 2000;5(3):47-53.