

ORIGINAL ARTICLE

Combined laser acupuncture and desmopressin for treating resistant cases of monosymptomatic nocturnal enuresis: A randomized comparative studyESSAM ELDIN S. MOURSY¹, NAGLAA F. KAMEL² & AHMED F. KASEEM³¹*Urology Department, Sohag Faculty of Medicine, Sohag, Egypt,* ²*Physiotherapy Department, Sohag General Hospital and Ibn Sina Hospital, Sohag, Egypt,* and ³*Neurology Department, Sohag General Hospital, Sohag, Egypt***Abstract**

Objective. Monosymptomatic nocturnal enuresis (MNE) is a common sociomedical problem affecting children that may persist until adulthood despite various lines of therapy. The aim of this study was to assess the efficacy of combined laser acupuncture and desmopressin in managing patients with resistant MNE, compared with their efficacy when used as monotherapy. **Material and methods.** The study included 186 patients with a mean age of 15.7 years (range 10–21 years) presenting with persistent MNE. All patients were evaluated clinically and investigated with urine analysis, plain X-ray of the urinary tract and abdominal ultrasonography. They were randomized into three equal groups based on the line of management: group A, managed with laser acupuncture alone; group B, managed with desmopressin alone; and group C, managed with a combination of laser acupuncture and desmopressin, with a treatment course of 3 months and follow-up period of 6 months to record the efficacy of therapy, side-effects and bladder capacity. **Results.** A statistically significant higher cure rate was reported in group C patients, being reported in 33, 35 and 46 patients in groups A, B and C, respectively. Improvement was reported in 18, 17 and 13 cases in groups A, B and C, respectively, but the difference was not statistically significant. Bladder capacity significantly increased only in patients receiving acupuncture (groups A and C). **Conclusion.** Combined laser acupuncture and desmopressin is a promising and valid option to manage resistant cases of MNE.

Key Words: *desmopressin, laser acupuncture, monosymptomatic nocturnal enuresis.***Introduction**

Monosymptomatic nocturnal enuresis (MNE) is defined as involuntary urine voiding during sleep at least twice per week for at least three consecutive months in a child over 5 years of age and not due to either a drug side-effect or a medical condition [1]. It has an incidence of 15–25% by the age of 5 years, which decreases by the age of 12 to 8% and 4% in boys and girls, respectively [2]. It is considered not only a medical problem but also a distressing psychosocial problem for the child and his or her family.

The exact cause of MNE is still obscure and the line of management has not been standardized. It is mainly managed with wetting alarms, medical pharmaceutical agents such as desmopressin, tricyclics or

oxybutynin [3], and alternative treatment modalities such as biofeedback, acupuncture and hypnotherapy [4]. Despite all these modalities, some patients remain unresponsive to treatment through adulthood in the absence of any organic cause, representing a major challenge to physicians. To manage these patients, desmopressin has been recommended either alone or in combination with anticholinergics (oxybutynin) [5], while other authors reported the use of laser acupuncture [6]. The exact mechanism of the acupuncture is not fully understood but it is believed to induce dermal stimulation on local acupuncture points [7], with the aim of normalizing bladder function [8].

The aim of this work was to assess the efficacy of a combined therapy of laser acupuncture and

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desmopressin to manage patients with persistent nocturnal enuresis, comparing the outcome with their efficacy when used as monotherapy.

Material and methods

Between June 2011 and July 2012, 192 patients (108 boys and 84 girls) with a mean age of 15.7 years (range 10–21 years) presented to the urology outpatient clinics of university hospital and Ibn Sina hospital in Sohag, Egypt. All patients had persistent nocturnal enuresis, wetting the bed on more than 2 nights per week, with a past history of failed medical treatment using anticholinergics (oxybutynin) twice daily for 3 months with either no response (76 patients) or relapse after cessation of therapy (116 patients). An interval of at least 6 months was left before patients were included in the study, giving a chance for the efficacy of the initial treatment to be revealed.

All patients were evaluated clinically for other urological or neurological disorders and investigated with urine analysis, plain X-ray of the urinary tract and abdominal ultrasonography. Urodynamic study was not routinely performed unless a neuropathic disorder, urgency or bladder dysfunction was clinically suspected.

Maximum voided volume (MVV) was measured in all patients using a voiding diary over 4 days before starting therapy (excluding the morning voids).

Patients with evidence of urinary tract infections, bladder dysfunction, psychological or neurological disorders or other organic disorders were excluded from the study to be managed accordingly (six patients).

Based on the line of management, computer-generated random numbers were used to randomly allocate the remaining 186 patients into three equal sized groups: group A, managed with laser acupuncture monotherapy; group B, managed with desmopressin monotherapy; and group C, managed with combined therapy of laser acupuncture and desmopressin.

Desmopressin was administered sublingually as a per-night dose of 120 µg once daily for 3 months. Acupuncture was administered twice weekly for 3 months using an infrared (gallium aluminium arsenide) laser at a wavelength of 808 nm and a power of 200 mW applied for 26 s to produce energy of less than 4 J/cm. Acupuncture was applied at the following points: REN2, REN3, REN4, SP6, ST29, ST36, UB23, UB28, UB32 and UB40 (Figure 1).

The study was performed after receiving ethics committee approval from the institute. Informed consent was obtained from all patients or their parents after discussing the details of the proposed management with them.

Evaluation and follow-up

The study period was 9 months (3 months as a treatment course and 6 months as follow-up after cessation of treatment), during which the patients were evaluated once every 2 weeks for 3 months and once every 4 weeks for 6 months. During each visit, the patients were assessed clinically to report voiding patterns and any side-effects, and also assessed sonographically for bladder capacity and residual urine. The patients were asked to record their wet and dry nights on a calendar throughout the study period and to record post-treatment MVV

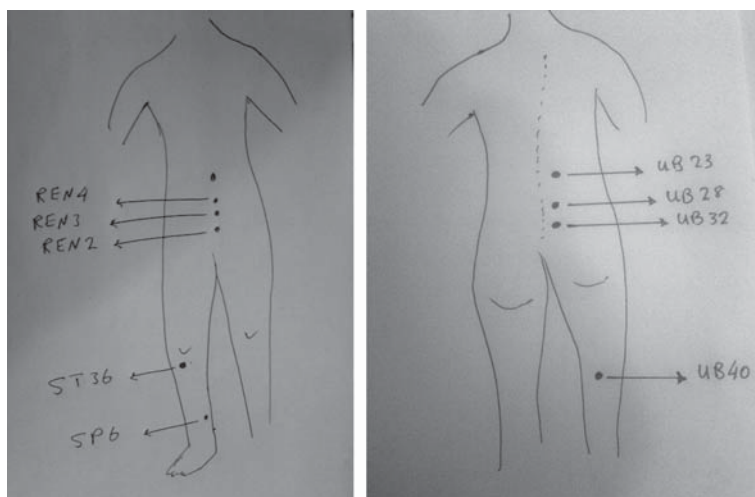


Figure 1. Acupuncture points.

Table I. Patients' characteristics.

	Group A	Group B	Group C	<i>p</i>
	(<i>n</i> = 62)	(<i>n</i> = 62)	(<i>n</i> = 62)	
Age (years), mean (range)	15.6 (10–21)	15.9 (11–21)	15.8 (11–21)	> 0.05
Gender				
Male	38	37	39	
Female	24	25	23	
Weekly wet nights, mean ± SD	4.735 ± 1.07	4.731 ± 1.19	4.721 ± 1.16	
MVV (ml)	233	254	247	

MVV = maximum voided volume.

for 4 days per month after cessation of therapy, using a voiding diary.

The response to treatment was defined as cure if enuresis disappeared without relapse within the next 6 months, improvement if there was more than a 50% decrease in the wet nights per week, and treatment failure if there was less than a 50% decrease in the wet nights or if the problem remained unchanged or worsened.

Statistical analysis

Data are expressed as the mean, SD and range. The measured outcomes were compared using chi-squared tests for categorical variables and analysis of variance (ANOVA) tests for multivariate analysis using SPSS 16.0 (SPSS, Chicago, IL, USA) software. A *p* value less than 0.05 was considered statistically significant.

Results

The study included 186 patients with a mean age of 15.7 years who presented with persistent MNE after unsuccessful treatment with anticholinergics (oxybutynin).

The patients were randomized into three groups based on the line of management. Patients' characteristics are shown in Table I. The distribution of the study population across the age groups is presented in Table II, which shows that most of them lay in the age group between 10 and 14 years (104 patients).

Table II. Study population across age groups.

Age (years)	Group A	Group B	Group C	Total
10–12	19	20	19	58
12–14	16	15	15	46
14–16	11	10	12	33
16–18	9	9	10	28
>18	7	8	6	21
Total	62	62	62	186

There were no statistically significant differences between groups in age, gender, MVV or the mean number of weekly wet nights. MVV in relation to age groups is shown in Table III.

Six months after treatment, cure with no bed wetting was recorded in 33 (53%), 35 (56.5%) and 46 (74%) patients in groups A, B and C, respectively, while no response was reported in 11 (18%), 10 (16%) and three (5%) patients in groups A, B and C, respectively, with a statistically significant higher cure rate in group C patients (*p* < 0.05). The difference in cure rate between groups A and B was not statistically significant (*p* > 0.05) (Table IV).

Improvement was reported in 18, 17 and 13 cases in groups A, B and C, respectively, with the mean weekly number of wet nights reducing from 4.735 to 2.3 in group A patients, from 4.7143 to 2.1 in group B patients and from 4.721 to 1.9 in group C patients. However, the difference was not statistically significant (*p* > 0.05) (Table V).

On assessing the post-treatment MVV (Table VI) in addition to the estimated age-related MVV (Table VII), it was found that it significantly increased only in groups A and C patients compared to pretreatment values and compared to group B patients (Tables VI and VII). None of the patients demonstrated postvoiding residual urine.

Table III. Maximum voided volume (MVV) before treatment in relation to age groups.

Age (years)	Group A	Group B	Group C	<i>p</i>			
(years)	<i>n</i>	MVV	<i>n</i>	MVV	<i>n</i>	MVV	
10–12	19	195	20	220	19	215	> 0.05
12–14	16	215	15	235	15	235	
14–16	11	230	10	255	12	250	
16–18	9	250	9	270	10	260	
>18	7	275	8	290	6	275	
Mean	62	233	62	254	62	247	

Table IV. Cure rate after treatment.

	Group A	Group B	<i>p</i>	Group C	<i>p</i>
Cure	33 (53)	35 (56.5)	> 0.05	46 (74)	< 0.05
Improvement	18 (29)	17 (27.5)		13 (21)	> 0.05
No response	11(18)	10 (16)		3 (5)	< 0.05
Total	62	62		62	

Data are shown as *n* (%).

Table V. Improvement after treatment.

	Before treatment	During treatment	After treatment
Group A	4.735 ± 1.07	1.7 ± 1.11	2.3 ± 1.21
Group B	4.731 ± 1.19	1.6 ± 1.22	2.1 ± 1.19
Group C	4.721 ± 1.16	1.1 ± 1.18	1.9 ± 1.14

Data are shown as mean ± SD.

Table VI. Pre and post-treatment maximum voided volume before and after treatment.

	Before treatment	After treatment	<i>p</i>
Group A	233 ± 30.943	340 ± 47.04	< 0.05
Group B	254 ± 27.7	286 ± 27.7	> 0.05
Group C	247 ± 23.08	346 ± 42.49	< 0.05

Data are shown as mean ± SD.

Patients showing failure (24 patients) or partial response (48 patients) were further managed with a second course of combination therapy of desmopressin (at a higher dose of 240 g) and acupuncture with a further 6 months of follow-up. Cure was achieved in 38 out of 72 of these patients (53%) while improvement was reported in 21 patients (29%). Thirteen patients (18%) did not respond.

No side-effects were experienced throughout the treatment course.

Discussion

MNE is a distressing sociomedical problem with unknown aetiology. Nocturnal polyuria, inability to

wake up and a constitutionally small bladder are suspected causative factors [9]. Anticholinergics, desmopressin and wetting alarms can all be used in management, with respective success rates of 45% [5], 48% [10] and 65% [11].

However, the drugs may be associated with some side-effects that cause parents to be reluctant to use them for long periods. Wetting alarms are noisy and may embarrass patients, who usually prefer to keep their condition secret. Moreover, some patients remain unresponsive to all these management options, with a negative impact on their self-esteem and performance [12,13].

In this study, traditional Chinese acupuncture was used to manage those non-responders either as monotherapy (group A) or in combination with desmopressin (group C), comparing the outcome with a third group of patients managed with desmopressin monotherapy (group B). The study included 186 patients with a mean age of 15.7 years (range 10–21 years), so the patients were old enough to be cooperative, compliant and not afraid of acupuncture, and to have a strong desire to be cured.

Desmopressin was administered as a per-night 120 g lyophilisate sublingual dose (MELT). The lyophilisate rather than tablet form was preferred as it has a similar efficacy to tablets but at a lower dose, facilitating its safe use at a younger age [14,15]. Ferrara et al. reported the use of oral desmopressin lyophilisate to manage 103 cases of MNE at an initial dose of 120 g for 3 months, followed by gradual dose reduction [10]. Montaldo et al. observed no significant difference in patients' response between the 120 g and 240 g doses of desmopressin lyophilisate and they increased the dose to 240 g in patients showing no or partial response to the 120 g dose [5].

Laser acupuncture was administered as an infrared laser at an energy of less than 4 J/cm. This amount of energy is suitable for nerve regeneration and stimulation. A higher energy is recommended when pain relief is desired [16–18]. The laser was applied at the points REN2, REN3, REN4, SP6, ST29, ST36, UB23, UB28, UB32, UB40 and H7, which are the

Table VII. Age-related maximum voided volume (MVV) before and after treatment.

Age (years)	Group A			Group B			Group C		
	<i>n</i>	Before	After	<i>n</i>	Before	After	<i>n</i>	Before	After
10–12	19	195	270	20	220	250	19	215	285
12–14	16	215	325	15	235	270	15	235	330
14–16	11	230	340	10	255	285	12	250	345
16–18	9	250	375	9	270	305	10	260	375
>18	7	275	390	8	290	320	6	275	395
Mean	62	233	340	62	254	286	62	247	346

usual points reported by many authors to manage urinary complaints including enuresis [19–21].

Heller et al. used acupuncture over 3 months to treat children with MNE at the points of medial Ren 3, bilateral Ma 36, bilateral Mi 6, bilateral Bl 33, medial Ren 6 and medial Ex B5, and reported a better enuresis frequency in 87.5% of their patients [19]. Yuksek et al. applied acupuncture at the points of Gv4, Gv15, Gv20, B23, B28, B32, H7, H9, St36, Sp4, Sp6, Sp12, Ren2, Ren3, Ren6, K3 and K5 [20].

In the present series, a cure rate of 53%, 56.5% and 74% was reported in groups A, B and C, respectively. Considering the 15% yearly spontaneous cure rate among enuretic patients, these results suggest that both desmopressin and acupuncture, either as a monotherapy or as combined therapy, have a role in managing resistant cases of MNE.

This is supported by the series of Björkström et al. [21], who studied the efficacy of electroacupuncture applied in 25 children who had previously been treated for nocturnal enuresis. At the 6-month follow-up, five children had a complete response and six had a partial response. A similar study was reported by Serel et al. [22], who assessed the therapeutic efficacy of acupuncture in treating 50 patients with primary persistent nocturnal enuresis, and reported a 86% complete response (in 43 out of 50 cases). Yuksek et al. compared the efficacy of acupressure versus oxybutynin in managing MNE and reported a better outcome with the use of acupressure, with complete and partial responses of 83.3% and 16.7%, respectively, with acupressure, and 58.3% and 33.3%, respectively, with oxybutynin [20].

In contrast, Radvanska et al. carried out a placebo-controlled study to assess the efficacy of laser acupuncture in managing 31 enuretic patients with an MVV of less than 70% of normal, and they observed no significant differences in the outcome between their three groups [23]. The selection of patients with bladder capacity of less than 70% of normal and/or different acupuncture technique (laser light was applied for a shorter duration across a greater number of acupuncture points) may explain the difference in response reported in this study. Moreover, the number of patients was too small to reach solid conclusions regarding the efficacy of treatment.

The efficacy of desmopressin in managing resistant cases of MNE was studied by Moffatt et al. [24], but the response was reported to be temporary, with relapse after cessation of therapy in the majority of cases.

In the current series, a better response was achieved using a monotherapy of desmopressin than acupuncture (63% versus 53%), although the difference was

not statistically significant. The cure rate was significantly better among patients receiving the combined therapy (group C).

Bower and colleagues [25] undertook a systemic review of the use of acupuncture to manage enuretic children, and observed a better response when acupuncture was combined with Chinese herbal remedies than when used as a single treatment modality.

Although the exact mechanism of acupuncture is still obscure, it is suggested to act through increasing the nocturnal bladder capacity. Honjo et al. [26] reported the use of acupuncture in managing 15 patients with MNE and compared the bladder capacities and weekly number of wet nights before and after treatment. They found a statistically significant increase in nocturnal bladder capacity in responders (from 201 ml to 334 ml). A similar finding was also observed in the present series, with a significant increase in bladder capacity in patients receiving acupuncture treatment. This finding may explain the synergistic effect of the combined therapy among these patients, as desmopressin decreases urine output while acupuncture increases bladder capacity.

An additional advantage to acupuncture treatment is the rarity of reported side-effects, providing an attractive option to parents [27] and a safe therapy for patients. In the present series, all patients tolerated the course of treatment, with no observed side-effects during the study period.

In conclusion, combined acupuncture and desmopressin is an attractive and promising modality for managing resistant adolescent cases of MNE. However, additional research is needed to establish a sound scientific protocol for their use.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Primary care Washington, DC: American Psychiatric Association; 1995.
- [2] Wan J, Greenfield S. Enuresis and common voiding abnormalities. *Pediatr Clin North Am* 1997;44:1117–31.
- [3] Dogan HS, Akpınar B, Gurocak S, Akata D, Bakkaloglu M, Tekgul S. Non-invasive evaluation of voiding function in asymptomatic primary school children. *Pediatr Nephrol* 2008;23:1115–22.
- [4] Van Poecke AJ, Cunliffe C. Chiropractic treatment for primary nocturnal enuresis: a case series of 33 consecutive patients. *J Manipulative Physiol Ther* 2009;32:675–81.
- [5] Montaldo P, Tafuro L, Rea M, Narciso V, Iossa AC, Del Gado R. Desmopressin and oxybutynin in monosymptomatic nocturnal enuresis: a randomized, double-blind,

- placebo-controlled trial and an assessment of predictive factors. *BJU Int* 2012;110:E381–6.
- [6] Radmayr C, Schlager A, Studen M, Bartsch G. Prospective randomized trial using laser acupuncture versus desmopressin in the treatment of nocturnal enuresis. *Eur Urol* 2001;40:201–5.
- [7] Jayasuriya AJayasuriya A. *Clinical acupuncture. Urogenital diseases*. 3rd ed. Sri Lanka: Plata Press; 1981. p 272.
- [8] Berman BM. Clinical applications of acupuncture: an overview of the evidence. *J Altern Complement Med* 2001;7:S111–18.
- [9] Wright A. Evidence-based assessment and management of childhood enuresis. *Pediatr Child Health* 2008;18:561–7.
- [10] Ferrara P, Romano V, Cortina I, Ianniello F, Fabrizio GC, Chiaretti A. Oral desmopressin lyophilisate (MELT) for monosymptomatic enuresis: structured versus abrupt withdrawal. *J Pediatr Urol* 2014;10:52–5.
- [11] Kamperis K, Hagstroem S, Rittig S, Djurhuus JC. Combination of the enuresis alarm and desmopressin. Second line treatment for enuresis nocturna. *J Urol* 2008;179:1128–31.
- [12] Egemen A, Akil I, Canda E, Ozyurt BC, Eser E. An evaluation of quality of life of mothers of children with enuresis nocturna. *Pediatr Nephrol* 2008;23:93–8.
- [13] Hjalmas K, Arnold T, Bower W, Caione P, Chiozza LM, von Gontard A, et al. Nocturnal enuresis: an international evidence based management strategy. *J Urol* 2004;171:2545–61.
- [14] De Guchteneere A, Van Herzeele C, Raes A, Dehoorne J, Hoebeke P, Van Laecke E, et al. Oral lyophilisate formulation of desmopressin: superior pharmacodynamics compared to tablet due to low food interaction. *J Urol* 2011;185:2308–13.
- [15] Lottmann H, Froeling F, Alloussi S, El-Radhi AS, Rittig S, Riis A, et al. A randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis. *Int J Clin Pract* 2007;61:1454–60.
- [16] Bradley PF. *Laser basics: principles of low intensity laser therapy (LILT)*. Presented at 3rd Annual Conference of the North American Association for Laser Therapy. Bethesda, Maryland, USA; 2003.
- [17] Tuner J, Hode L. *Laser therapy: clinical practice and scientific background*. Gransgesberg: Prima Books; 2002.
- [18] Blahnik JA, Rindge DW. *Laser therapy: a clinical manual*. Melbourne, FL: Healing Light Seminars; 2003.
- [19] Heller G, Langen PH, Steffens J. Laser acupuncture as third-line therapy for primary nocturnal enuresis. First results of a prospective study. *Urologe A* 2004;43:803–6.
- [20] Yuksek MS, Erdem AF, Atalay C, Demirel A. Acupressure versus oxybutinin in the treatment of enuresis. *J Int Med Res* 2003;31:552–6.
- [21] Björkström G, Hellstrom AL, Andersson S. Electro-acupuncture in the treatment of children with monosymptomatic nocturnal enuresis. *Scand J Urol Nephrol* 2000;34:21–6.
- [22] Serel TA, Perk H, Koyuncuoglu HR, Kosar A, Celik K, Deniz N. Acupuncture therapy in the management of persistent primary nocturnal enuresis preliminary results. *Scand J Urol Nephrol* 2001;35:40–3.
- [23] Radvanska E, Kamperis K, Kleif A Kovács L, Rittig S. Effect of laser acupuncture for monosymptomatic nocturnal enuresis on bladder reservoir function and nocturnal urine output. *J Urol* 2011;185:1857–61.
- [24] Moffatt ME, Harlos S, Kirshen AJ, Burd L. Desmopressin acetate and nocturnal enuresis: how much do we know? *Pediatrics* 1993;92:420–5.
- [25] Bower WF, Diao M, Tang JL, Yeung CK. Acupuncture for nocturnal enuresis in children: a systematic review and exploration of rationale. *NeuroUrol Urodyn* 2005;24:267–72.
- [26] Honjo H, Kawauchi A, Ukimura O, Soh J, Mizutani Y, Miki T. Treatment of monosymptomatic nocturnal enuresis by acupuncture: a preliminary study. *Int J Urol* 2002;9:672–6.
- [27] Monda JM, Husmann DA. Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate and bedwetting alarm systems. *J Urol* 1995;154:745–8.