



Acupuncture as a treatment for nocturnal enuresis

W.F. Bower^{a,*}, M. Diao^{b,1}

^a Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China

^b Department of Pediatric Surgery, The Capital Institute of Pediatrics, Beijing, China

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ABSTRACT

Acupuncture can influence spinal micturition centers and parasympathetic innervation to the urinary tract and is known to modulate brain function via the descending serotonergic system. There are numerous difficulties in evaluating the efficacy of acupuncture in patients with nocturnal enuresis (NE), since the patient group is frequently heterogenous and the intervention is commonly given in association with other modalities. Until recently incomplete reporting of the quality aspects of studies has also limited evaluation of treatment effects.

The aim of this study was to systematically evaluate reports from both Western and Eastern medicines in which acupuncture was compared to some other treatment modality in children with nocturnal enuresis. Focusing on Chinese language sources 41 new studies of acupuncture for NE were identified, 13 of which were clinical trials that reported parameters of treatment and defined outcome measures of efficacy. A standardized data extraction form was used to evaluate outcome measures and to scrutinize the quality aspects of studies.

All but one study reported the efficacy rate of acupuncture as part of a TCM package to be higher than alarm therapy, the gold standard of Western medicine intervention for NE. Acupuncture as a monotherapy for the treatment of NE appears to be less effective than acupuncture given as part of a combined Traditional Chinese Medicine approach. Electroacupuncture enhances treatment outcomes.

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1. Background to nocturnal enuresis

Nocturnal enuresis (NE) is defined as emptying of the bladder during sleep irrespective of the age of the individual or the severity of episodes (Nevéus et al., 2006). Enuresis in children without any other lower urinary tract (LUT) symptoms or history of bladder dysfunction is sub-classified as monosymptomatic (Nevéus et al., 2006). Conversely non-monosymptomatic enuresis denotes the coexistence of any of the symptoms of increased or decreased voiding frequency, incontinence, urgency, hesitancy, straining, weak or intermittent urine flow, incomplete emptying, post void dribble or dysuria (Nevéus et al., 2006). The onset (primary if child has never been dry for at least 6 months, and secondary when initial reliable night dryness that has been lost) is not diagnostically relevant but may be clinically important in establishing pathogenesis.

Nocturnal enuresis is a heterogenous disorder of varying severity whose underlying aetiology is strongly associated with genetic factors but shows no clear genotype-phenotype association (Hjalmas et al., 2004). NE is inherited as a dominant trait with high penetrance (Arnell

et al., 1997; Bakwin, 1971) with the genetic risk high for both individuals with and without co-existing LUT symptoms (Loeys et al., 2002; von Gontard et al., 1996). Detrusor muscle overactivity during the night is implicated (Yeung et al., 2004a,b), either as a result of altered brainstem control mechanisms or secondary to functional outlet obstruction (Birder et al., 2009). Similar overactivity during the day is associated with the lower urinary tract symptoms of small voided volumes and a reduced functional bladder capacity (Kruse et al., 1999). Asian researchers have identified the presence of nocturnal detrusor instability in up to one third of all enuretic children (Watanabe et al., 1997; Watanabe, 1995) and 44% of patients whose NE failed to respond to standard treatment (Yeung et al., 1999; Yeung et al., 2002).

Enuretic children may sleep normally but be unable to suppress nocturnal detrusor contractions or awaken in response to them or to the sensation of bladder fullness (Nijman et al., 2005). Recently low bladder capacity in children with severe nocturnal enuresis has been shown to correlate with a high sleep arousal threshold and less frequent arousal episodes, suggesting impairment of the bladder–brain dialogue (Yeung et al., 2005).

Renal urine production and its circadian rhythm contributes to NE. Diuresis during sleep should approximate 50% of daytime levels (Rittig et al., 1995) and be regulated by free water excretion (arginine vasopressin, AVP) or solute excretion (angiotensin II and aldosterone) (Nijman et al., 2005). Scandinavian studies have demonstrated that two thirds of patients with monosymptomatic NE produce large amounts of

* Corresponding author. Department of Surgery, 4th Floor Clinical Sciences Building, Prince of Wales Hospital, Shatin, NT, Hong Kong, China. Tel.: +852 2637 2469; fax: +852 2637 7581.

E-mail address: wfbower@hotmail.com (W.F. Bower).

¹ These authors contributed equally to this study.

nocturnal urine, exceeding bladder capacity (Norgaard et al., 1985; Rittig et al., 1989). It is not known whether these patients have impaired renal sensitivity to vasopressin or require supranormal levels to achieve a circadian rhythm of urine production. NE children with nocturnal polyuria may also have sodium retention that generates hypovolaemia and inhibits vasopressin production (Dehoorne et al., 2006; Kamperis et al., 2006). A further confounder is that NE children with nocturnal polyuria may well have coexisting reduced bladder capacity (Yeung et al., 2004a,b).

The interplay of pathological changes in children with nocturnal enuresis remains elusive. There is clearly a mismatch between nocturnal urine production volume, bladder functional capacity and a disturbance of arousal mechanisms. Not all disturbances are present in each patient and the relative vulnerability to each remains largely undetermined. The only independent variables conclusively associated with nocturnal enuresis are non-pathophysiological and include gender (males more at risk), a positive family history and co-existing behavioural problems (Cher et al., 2002; Fergusson et al., 1986).

2. Treatment options for nocturnal enuresis

The most common Western medicine single therapies for children with nocturnal enuresis are either the bedwetting alarm to facilitate arousal from sleep or synthetic antidiuretic hormone to reduce the volume of overnight urine. Alarm therapy has a 43% lasting cure rate (Glazener et al., 2005) and is most effective in children with monosymptomatic enuresis. Children with nocturnal polyuria and few wet nights per week respond best to antidiuresis.

Other common monotherapies for enuresis are antimuscarinic medication, urotherapy and acupuncture. Antimuscarinic drugs may be trialed in enuretic children suspected of having nocturnal detrusor overactivity or as a first line during the day in non monosymptomatic enuresis. Urotherapy, or rehabilitation of bladder mechanics, is most helpful in children with associated LUT symptoms but has little to offer the individual with monosymptomatic enuresis. Acupuncture as a primary therapy is common in Chinese, Korean and Japanese medicine although less well understood in Western medicine. A recent systematic review identified reporting issues that limited evaluation of quality aspects of studies reported, but none the less concluded that there was evidence of a positive effect of acupuncture on nocturnal enuresis (Bower et al., 2005).

Efficacy of traditional Chinese acupuncture for nocturnal enuresis has been reported to range from 76% to 98% (Tuzuner et al., 1989; Zhong, 1986), a markedly higher cure rate than any of the other single therapies. Western acupuncture studies report a positive effect upon the number of enuresis episodes, the storage capacity of the bladder and the ease of rousing from sleep to void (Honjo et al., 2002; Bjorkstrom et al., 2000). Where there is urodynamic evidence of detrusor overactivity, acupuncture therapy has been reported to suppress uninhibited bladder contractions and to significantly improve wetting (Minni et al., 1990; Kachan et al., 1993).

In clinical practice therapies are combined for children with NE who do not respond to a single treatment modality. While this can effectively address the individual's underlying dysfunction, no guidelines have been published to direct selection of combination therapy.

3. Rationale for acupuncture improving Nocturnal Enuresis

Acupuncture points used to treat bladder dysfunction are located in areas that coincide with innervation by spinal sacral segments S₂ through to S₄ and stated in the treatment protocols. The points of BL 23, BL 28, BL 32, RN 3, RN 4, RN 6, RN 12 influence the spinal micturition centers and parasympathetic innervation to the urinary tract (Minni et al., 1990; Sun, 2000), while stimulation on scalp acupoints of DU 20 and DU 14 modulate brain function via the inner temporal, thalamencephalon and prefrontal cortical systems (Sun, 2000; Huang et al.,

2007). Stimulation of acupoints UB 20, UB 13, SP 6, ST 36, KI 3 and LU 9 are considered to invigorate spleen, vital energy and blood which facilitate normalized bladder function. Treatment consists of 1–6 courses of 10–15 sessions of needle insertion, pressure, heating or the application of electric current percutaneously at selected acupoints. There is a high concentration of neuroendocrine transmitters and hormones at acupuncture points, which release and spread after needling and other stimulation (Omura 1989; Kashiba and Ueda, 1991).

Electro-acupuncture, the application of a pulsating electrical current to acupuncture needles to further stimulate the acupoints, was developed in China as an extension of hand manipulation of acupuncture needles around 1934 (CATCM 1975). The procedure involves inserting the needle as per conventional acupuncture to achieve the qi reaction with manual stimulation, then delivered electrical stimuli through the needles, using biphasic square-shaped pulses with low frequency. The current is of painless intensity but produces moderate muscle spasms. Individual sessions last less than 30 minutes.

The benefits of electro-acupuncture relate to being able to standardize the intervention. A continuous stimulation can be guaranteed so that fatigue of practitioners performing manual manipulation does not influence treatment dosage. The frequency and intensity of stimulation can also be standardized, a goal hard to attain with hand maneuvering. The treatment dosage can be objectively recorded, assessed and adjusted according to the patient's condition, making a standard acupuncture intervention protocol possible. The practitioners can conduct the treatment for different patients simultaneously and can programme stronger stimulation for some complicated cases (neuralgia, paralysis etc.) without causing tissue damage that may be induced by twirling and lifting and thrusting the needle. The main drawback of electro-acupuncture is that it cannot be connected to all acupoints.

Our review of Chinese acupuncture literature indicates that electro-acupuncture can effectively impact NE and that adjunctive electro-stimulation enhances the treatment outcomes when comparing to manual acupuncture alone (Ma and Tang, 2005). However, to our knowledge there is no RCT comparing manual and electro-acupuncture, evidence of difference in efficacy is awaited.

While frequency and duration electric stimuli are commonly reported, few studies describe the details of current intensity. Most authors report “painless intensity with moderate muscle spasms” or “pain within the patient's tolerance”. Hence, it is difficult to evaluate the effective intensity for NE patients in different age groups, disorder subtypes, levels of symptom severity. No guidelines are available to tailor the intensity in relation to response to treatment.

4. Evidence of efficacy of TCM acupuncture for nocturnal enuresis

Functional magnetic resonance imaging (fMRI) and PET scan during natural or conventional bladder filling in healthy subjects showed activation of the brain regions of pons, midbrain periaqueductal gray, thalamus, hypothalamus and frontal cortex (Matsuura et al., 2002). During acupuncture at ST 36, fMRI indicates activation in hypothalamus and bilateral prefrontal cortex (Wu et al., 1999), suggesting acupuncture utilizes the neural brainstem–thalamus–cortex reticular system. Sustained activation of hypothalamus was noted as were increased concentrations of neurotransmitters, such as 5-HT (Wu et al., 1999; Yoshimoto et al., 2006). Acupuncture may thus affect micturition or arousal through the descending serotonergic system. Simultaneous EEG and cystometric monitoring in urethane anesthetized male rats undergoing acupuncture showed that after acupuncture stimulation on the sacral segment, bladder activity was suppressed in 53% (36/68) trials, and that in 61% (22/36) of animals this was accompanied by an increased EEG amplitude (Tanaka et al., 2002).

In addition to the effects of manual acupuncture, electro-acupuncture may induce additional electrophysiological responses. It is likely that three efferent pathways transmit facilitatory or inhibitory signals from higher CNS center to the pontine center and sacral motor neurons.

Table 1
Characteristics of acupuncture trials for nocturnal enuresis identified in the Chinese language literature since our last review.

Author	Treatment 1	Cure 1 (%)	Treatment 2	Cure 2 (%)	Length of follow-up (months)
Hong et al. (2008)	Bird-pecking needling—12 days	26/37 (70.2)	Needle warming moxibustion—12 days	23/37 (62.2)	3
Zhang Ai-Xian (2008)	Electro-acupuncture and atropine injection—18 days	17/31 (54.8)	Electro-acupuncture—18 days	20/30 (66.6)	6
Wang and Wang (2008)	Oxybutinin, laser acupuncture, urotherapy—AP 7 days, other 3 months	23/30 (76.6)	Oxybutinin—3 months	18/30 (60)	3
Lin Gui-Jin (2007)	Acupuncture and moxibustion—duration unclear	24/38 (63.1)	Acupuncture—duration unclear	11/32 (34.4)	1
Cheng Shen (2008)	Vitamin B injection on acupoints—10 days	78/80 (97.5)	Imipramine—duration not stated	62/70 (88.6)	Nil
Liu et al. (2006)	Acupuncture and moxibustion—28 days	37/41 (90.2)	Acupuncture—28 days	22/31 (71)	1
Hong and Gao (2006)	Acupuncture—30 days	24/30 (66.6)	Acupuncture on different points—30 days	10/24 (41.6)	1
Ding Xi-Rue (2005)	Acupuncture and cupping—20 days	15/20 (75)	TCM herbs and tonics—20 days	10/20 (50)	Nil
Dong Yang-Ying (2005)	Acupuncture, external herbal medicine—duration not stated	25/35 (71.4)	Acupuncture—duration not stated	19/34 (55.9)	Nil
Wen et al. (2001)	Acupuncture and herbal medicine—duration not stated	10/31 (32.2)	Acupuncture—duration not stated	1/30 (3.3)	6
Wang and Wang (2008)	Herbal medicine and auricular acupoints—30 days	13/28 (46.4)	Desmopressin—30 days	0/19 (0)	Nil
Qiao and Ren (2008)	Electro-acupuncture and acupuncture—60 days	23/40 (57.5)	Electro-acupuncture, acupuncture and herbal medicine—60 days	49/62 (79)	Nil
Xiao and Zhang (2001)	Scalp acupuncture and herbal medicine—20 days	40/43 (93)	Herbal medicine—20 days	31/41 (83)	Nil

These include the lateral reticulospinal tract which facilitates bladder contractile activity; the ventral reticulospinal tract which inhibits detrusor contraction; and the medial reticulospinal tract that induces external sphincter contraction (Zhao et al., 2009). Given that electrophysiological responses happen across the neuro-network area instead of at specific points, electro-stimulation may also improve the brain arousal/awakening area which partially overlaps with central micturition centers (Zhao et al., 2009).

There are a number of difficulties associated with understanding the effect of acupuncture on the lower urinary tract. Acupuncture is traditionally delivered as one of a number of strategies rather than as an individual therapy. The patient populations are frequently heterogeneous and may include neurological disorders and not differentiate between sub-classifications of nocturnal enuresis. The intervention can vary depending on the type of acupuncture used (needles, pressure, electrotherapy or in association with moxibustion), additional therapies, singular or multiple sites of application, the frequency of treatment sessions and the overall duration of therapy.

A systematic review of both Western and Eastern studies in which acupuncture was compared to some other treatment modality suggested encouraging results for children with enuresis, however, the quality of reporting limited identification of key parameters (Bower et al., 2005). As our previous review ended with studies from 2003, we extended the process and identified reports of acupuncture for the treatment of nocturnal enuresis from 2004 until 2010 and also added previously unidentified earlier studies. Unique to this search is the focus on Chinese language sources. Forty one new studies of acupuncture for NE were identified in the Chinese literature, of which 13 were clinical trials. The key characteristics of these studies are summarized in Table 1 (Hong et al., 2008; Xia 2005; Zhang 2008; Wang et al., 2008; Lin 2007; Cheng, 2008; Liu et al., 2006; Hong et al., 2006; Ding, 2005; Dong 2005; Wen et al., 2001; Wang et al., 2008; Qiao and Ren, 2008; Xiao and Zhang, 2001).

All studies included rigorously definitions of outcome measures and a description of the length of the post treatment period before evaluation of efficacy. It can be seen that 6 studies evaluated treatment effect immediately after intervention while the rest waited between 1 and 6 months. Authors accounted for all subjects and reported no drop-outs during the intervention.

With the exception of the Wen study (Wen et al., 2001), the efficacy rate of TCM (\pm acupuncture) was greater than that of alarm therapy in Western medicine. Wen reported only 1 subject to be cured 6 months after treatment, although 19 of the 21 other children treated were improved. One might expect investigator bias toward novel comparative therapies in these trials; however, acupuncture as the stand alone modality still had efficacy rates of up to 70%.

5. Evidence of efficacy of acupuncture for enuresis in Western studies

Much of the older data available in Western medicine publications have been obtained by clinicians with a primary interest in bladder disorders but limited knowledge and skill in applying Chinese medicine. Findings, however, suggest that a wide range of bladder disorders respond positively to acupuncture. We have identified 2 new trials and 4 cohort studies of acupuncture for nocturnal enuresis in a Western setting reported since our previous review (Yukseket al., 2003; Diao et al., 2008). Table 2 summarizes findings from the two randomized trials and reveals small numbers in both trials. The 2008 study is of interest since the electro-acupuncture was provided by a highly experienced TCM practitioner yet after 3 months only 50% of patients had achieved a 90% reduction in the number of wet nights. The acupuncture was administered as a monotherapy and was markedly less effective in resolving enuresis than any of the mainland reports of similar intervention.

6. Discussion

Both an international consensus on the management of nocturnal enuresis (Hjalmas et al., 2004) and a systematic review of the evidence of efficacy of acupuncture (Bower et al., 2005) found in favour of the treatment approach. Since then reports have added further tentative evidence that children who receive acupuncture can become drier at night. The size of the treatment effect, however, is unclear.

In this era of evidence-based medicine, efficacy is derived from randomized and controlled clinical trials that have inherently high levels of reporting about quality aspects of the studies. If data from such studies are considered of most value, the expectation is that scientific

Table 2
Acupuncture trials for nocturnal enuresis identified in Western literature since 2004.

Author	Treatment 1	Cure 1 (%)	Treatment 2	Cure 2 (%)	Length of follow-up (months)
Yukseket al. (2003)	Acupuncture points finger massaged—15 days to 6 months	10/12 (83.3)	Oxybutinin	7/12 (58.3)	6
Diao et al. (2008)	Electro-acupuncture—3 months	0/15 (0)	Desmopressin + enuretic alarm—3 months	4/20 (20)	3

findings will then drive clinical practice. In the arena of acupuncture this is clearly a flawed assumption given that the teams who run high quality studies often have minimal experience with the theoretical basis for administering acupuncture. Conversely, this is not a reason to accept findings from potentially biased and confounded studies reported by technical experts.

The specific problems with evaluating the effect of acupuncture in children with nocturnal enuresis are associated with heterogeneity of both the sample and the intervention being tested. According to the International Children's Continence Society standardization document (Nevéus et al., 2006), nocturnal enuresis falls into the two categories of monosymptomatic night wetting or enuresis accompanied by other symptoms of the lower urinary tract. The underlying aetiologies of these discrepant presentations mandate that the trialist separate children into these categories before testing an intervention and that the report of outcome be similarly specific.

An ideal study of acupuncture in nocturnal enuresis would require children be sub-classified as discussed above and then further grouped according to the number of initial wet nights per week (i.e. symptoms severity) and the age strata. Clearly younger children who are wet less often will appear to respond more to intervention and influence the size of treatment effect. Outcomes reported during treatment should be clearly stated and post-intervention measures reported along with longitudinal follow-up data. These measures would provide a level of transparency currently not evident in many reports.

In the conservative management of paediatric urological dysfunction the evaluation of monotherapies, given the clinical predominance of combination treatment, is a vexing issue. The bladder rehabilitation process of urotherapy, for example, is widely used to great effect but has not been evaluated by its component interventions. Pharmacotherapy, a mainstay of intervention for enuresis, frequently involves a combination of antimuscarinics and antidiuresis with some children also requiring alpha blocker or antibiotic medications. The possible combinations of polypharmacia are endless, and studies that scrutinize each combination do not exist. Given that clinicians routinely use treatment packages within the discipline of paediatric bladder management, the findings from acupuncture studies should resonate with actually clinical practice. Given that current intervention for enuresis addresses both behavioural and chemical pathways, the addition of acupuncture to influence neural mechanisms is logical. If the TCM theoretical basis necessitates multiple interventions to achieve optimal effect from acupuncture, then such therapies could become part of the multi-modal package that children are offered.

This necessitates evaluation of safety aspect of acupuncture and complementary therapies. TCM descriptions of acupuncture treatment for enuresis do not commonly report adverse events. A recent review of the safety of acupuncture in children noted that even though the actual risk to an individual patient was hard to determine there was likely to be a 1.55 risk of an adverse event in 100 treatments of acupuncture in a child. This was considered a low risk given 29 events occurred in 782 patients. The most common events were post-treatment sedation (32%), pain from the needles (26%), neuropathy (16%) and connective tissue changes (14%) (Jindal et al., 2008). It should be noted that this review considered studies in children with more severe disorders and illnesses than are observed in the healthy non-hospitalized enuretic population. Nonetheless, both side effects of treatment and practitioner error can occur in children receiving acupuncture for enuresis. Traumatic injury is rare but systemic effects, needling problems,

burns, infection and symptom aggravation can theoretically occur (White, 2004). Herbal medicines that often accompany acupuncture are little understood in the Western world and have not been extensively evaluated within that framework.

A more immediate limitation to the routine use of adjunctive acupuncture for nocturnal enuresis in wider clinical practice is the fear factor surrounding needles and puncturing the body. Children seen for this disorder range from 6 years of age through to the low teens and the routine use of needles in this age group would invoke fear of pain and parental concerns about safety and hygiene. Although the practice of acupuncture is spreading outside Asian countries, the treatment is still likely to be refused by parents in favour of less invasive primary therapies. In our own institution, in an ethnic Chinese population, we had experienced difficulty recruiting children to the acupuncture arm of studies. To address this limitation laser acupuncture and acupressure have both been proposed.

In summary, there is no dispute that peripherally applied acupuncture stimulates sensory nerves, increases the releases of neurotransmitters, neuropeptides and hormones, stimulates microcirculation, has an autonomic effect and up-regulates impulses to the spinal cord and ascending pathways to the brain (Cai, 1992; Shen, 2001). At present it is unknown whether the effects depend on the mode of stimulation or to more general effects of therapist attention, expectations, growth and development or even hope. Although the theoretical framework to support acupuncture having an impact on the urinary system is sound, reviewing all the evidence according to "scientific criteria", acupuncture cannot yet be considered a "proven" therapy.

In the real world, where medicine is not entirely "scientific", clinicians may consider adding an acupuncturist to the multidisciplinary team and including the therapy as one of the options to address lower urinary tract dysfunction in children. In adolescent or adult patients with unremitting enuresis, there are obvious benefits to be gained from a course of acupuncture that cannot be derived from the current treatment approaches. As with any intervention, the patients must be informed of possible, although unlikely, sequelae.

While there is probably minimal need to invest in large trials of acupuncture as a stand-alone therapy for enuresis, there is a dire need for transparent, high-quality studies of the efficacy of acupuncture in discrete groups of patients receiving "packages" of interventions for enuresis. TCM and acupuncture practitioners are encouraged to report methodology and findings in a way that convinces readers that sources of study bias have been minimized and to publish in the international literature. In this way acceptable evidence about the efficacy of acupuncture in treating nocturnal enuresis will accumulate and facilitate targeted and helpful treatment of this emotionally and socially debilitating disorder.

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