ORIGINAL ARTICLE

The Treatment of Primary Nocturnal Enuresis in Malaysia

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Summary

To determine treatment outcomes in Malaysian children with primary nocturnal enuresis using both non-pharmacological methods and oral desmopressin. Data was collected prospectively from children aged 6-18 years who were referred to the Hospital UKM Enuresis Clinic. Treatment was given to those with a baseline wetting frequency of at least six wet nights/ 14 nights. Three modalities were offered: fluid management, reward system and oral desmopressin. Response was recorded as partial (≥ 50% reduction in WN from baseline) or full (completely dry). Seventy-one healthy children completed 12 weeks of therapy. Twenty-three children (32.4%) responded to non-pharmacological methods alone (4 full and 19 partial). Another 37 children (51.2%) responded to oral desmopressin (32 to 0.2mg, 4 to 0.4mg and 1 to 0.6mg). Thirty-two percent became dry whilst on therapy. The mean wetting frequency during treatment was significantly reduced ($p<0.01$) compared to the baseline mean for both the non-pharmacological group and the desmopressin group. Discontinuation of desmopressin after 12 weeks increased the wetting frequency but this was still significantly lower than at baseline ($p<0.01$). No adverse events were recorded. Treatment of primary nocturnal enuresis in Malaysian children is both effective and well tolerated using fluid management strategies, reward systems and oral desmopressin

Key Words: Primary nocturnal enuresis, Non-pharmacological methods, Desmopressin

Introduction

Nocturnal enuresis (NE) is the involuntary voiding of urine in bed in a child aged five years or more in the absence of congenital or acquired defects of the nervous system or the urinary tract. It can be further categorized into primary (PNE) and secondary (SNE). Primary NE is when the child has been bedwetting from birth whilst children who have had a dry interval of six months or more and started bedwetting again are termed to have SNE. The definition for the frequency of wetting episodes reported in studies in the literature have been variable. The ICD –10 criteria (World Health Organisation, 1993)[1] uses at least one night per month whilst the DSM-IV criteria (American Psychiatry Association, 1995)[2] uses wetting of at least twice in a week. Hence reported prevalence rates differ greatly depending on the definitions used and the age of the populations screened. These studies however, indicate that the frequency of wetting clearly decreases as the child gets older. NE is more often seen in boys in the early years but equals out in later years, and it persists in about 1% of adolescents and adults[3-9]. Parental concern and/or child distress is rarely highlighted in the definitions though this plays a major part in deciding the clinical significance[10] of the problem particularly whether treatment options should be considered and if so, at what age it should be recommended.

In Malaysia, the only reported large epidemiological survey[11] indicates a prevalence rate for PNE of 6.2% in children aged 7 to 12 years using the ICD-10 criteria. This study also set out to determine the attitudes of

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Malaysian parents towards their child's enuresis and found that seventy-three percent considered it a problem, whilst 76% of the children admitted to being embarrassed by their bedwetting. Furthermore, 65% of parents requested further information and advice on treatment for their children hence confirming the need for an Enuresis Clinic in Kuala Lumpur.

The Hospital Universiti Kebangsaan Malaysia (HUKM) Enuresis Clinic was therefore set up and children from the 2001 survey were invited to attend, the initial purpose being to provide treatment for them. At a later date, new referrals from general practitioners and private paediatricians were received, many in the adolescent age group. Thus an opportunity to collect data prospectively and to evaluate effectiveness of treatment modalities was seen.

Materials and Methods

A database was set up to collect data from all children with nocturnal enuresis between the ages of 6 and 18 years who were referred to the HUKM Enuresis Clinic from August 2003. The objectives of the Clinic were to (i) obtain data on Malaysian enuretic children, (ii) provide information, advice and treatment options and (iii) to assess their response to the available therapeutic modalities.

At the first visit, a complete history was taken and physical examination was performed Table I. The history included a detail recall of the average daily fluid intake and micturition frequency. Urinalysis and radiological investigations were not performed unless there was a history suggestive of bacteriuria, irritable bladder or daytime incontinence. Constipation when present was treated and information in the form of a printed leaflet was given. The available options for therapy were then discussed. Each child was also given a wetting diary and instructed on recording a two week observation period to determine the baseline wetting frequency.

Three modalities of therapy were offered. These were: (1)Fluid Management (FM) which constituted a change in the daily drinking pattern with encouragement to drink as much as the child wanted during the morning and afternoons and cutting back on the late evening drinks particularly after dinner and pre-bedtime; (2) Reward System (RS) in which a Star Chart and simple rewards were given for dry nights. These rewards were pre-determined by both parents and child before they embarked on the program and the number of dry nights for which a reward was granted increased in a gradual stepwise fashion; and (3) oral desmopressin (DDAVP) –titrated to 0.2mg/0.4mg/0.6mg nightly. The bedwetting alarm system could not be offered during this time as these alarms were not readily available in Malaysia. Anticholinergic drugs such as imipramine and amitryptaline, were also not offered in this study.

At the second visit, the baseline wetting frequency was recorded from the wetting diary as number of wet nights per 14 nights (WN/14) and the child and/or parents chose one of the three options discussed. Those choosing the FM or RS options were seen at one month whist the DDAVP group were seen at two weekly intervals for dose titration. DDAVP was given as 0.2 mg tablet/s taken just before bed. The results were then recorded as the WN/14 for the two weeks preceeding each clinic visit. Partial responders (PR) were those achieving at least 50% reduction in WN/14 nights from baseline and a full responder (FR) was a child who became dry (zero WN). Responders (both PR and FR) continued in their chosen modality and completed a 12 week treatment period. Those on DDAVP were then given a further two weeks treatment-free period (wash-out). Non-responders to any one modality could choose to move to another treatment option, eg. FM to RS to DDAVP or FM to DDAVP. The outcome was recorded as PR or FR according to the frequency charted during the last two weeks of the 12 week treatment period and for those on DDAVP for the wash-out period as well.

Only children fulfilling the inclusion criteria stated in Table II were included in the data analysis. The Statistical Package for Social Sciences (SPSS 12.0) program was used and analysis was performed using the 2-tailed paired sample *t*-test.

Results

A total of 135 referrals aged between 6 and 18 years with nocturnal enuresis were seen at the HUKM Enuresis clinic from 1st August 2003 till 28th February 2006. Of these 17 did not fulfil the inclusion criteria (Figure 1); of the six with medical problems, one had morbid obesity with sleep obstructive apnoea syndrome and five were receiving medication from the child psychiatrist for various behavioural disorders. Of the remaining 118 children eligible for study, twenty-one defaulted follow-up after the initial visit, during

titration or during the treatment period. The majority of these could not be reached at their given addresses or contact numbers. Hence 71 children completed the 12 weeks treatment period and had complete data which could be analysed and another 26 children were still undergoing treatment at the time of this report.

The mean age was 9.84 years and there were almost equal number of boys and girls. Chinese children made up 48% of the group (Table III) and a positive family history of enuresis was obtained in less than half the referrals whilst it was not known in 5.6% including one adopted child. The mean number of WN during the baseline period for these 71 children was 11.62 /14 with more than half of them wetting every night. Twenty-three children (32.4%) had at least a 50% reduction in their wetting frequency by simple non-pharmacological methods alone (Figure 2a) and notably five were completely dry. The remaining 48 children elected for, or moved into the oral DDAVP treatment group.

All children in the DDAVP group started with 0.2mg per night (Figure 2b). A total of thirty-two children (71%) responded with 18 achieving FR and 14 PR. The remaining 16 children moved onto 0.4mg DDAVP per night. Of these, another 4 had PR whilst 12 had no response. Only one family elected to try 0.6mg and their child had PR.

Thus, 77% of the children on DDAVP therapy achieved at least a 50% reduction in WN with 18 becoming completely dry on treatment.

The overall mean wetting frequency during treatment reduced to 3.14WN/14. Using the paired samples t-test a significant difference was seen (Table IV). The 23 children receiving only FM and RS showed a remarkable clinical improvement in wetting frequency to a mean of 1.87 WN/14, which also achieved statistical significance. For the DDAVP group, the wetting frequency reduced during treatment from a mean of 12.08 WN/14 to 3.75 WN/14 and during the wash-out period to a frequency of 7.90 WN/14 which was still significantly lower than pre-treatment levels.

Figure 3 summarises the final treatment outcomes of the three modalities offered at this Enuresis Clinic. Thus, of the 71 children who completed this short course of therapy, 84.5% achieved at least a 50% reduction in their baseline wetting frequency with one-third achieving complete dryness. No adverse effects were reported in the DDAVP group.

Table I: Enuresis History and Examination

Dermographic history:
- age, sex, race, family history

Medical history:
- previous medical/surgical problems, drugs
- congenital CNS / UT disease
- family history of medical illness
- developmental milestones

Wetting history:
- primary / secondary enuresis
- wetting frequency
- exclude daytime urinary symptoms
- fluid intake diary – particularly the hours after dinner and before bedtime
- constipation and/or soiling
- previous therapy(including traditional medications)

Physical Examination:
- exclude CNS disease eg spinal dysraphism
- exclude genitourinary conditions
- exclude morbid obesity

Discussion

Nocturnal enuresis, a common childhood disorder showing similar prevalence rates in Malaysia as in other parts of the world[11] is generally regarded as a trivial, self-limiting problem that is expected to resolve spontaneously in the majority of cases. Forsythe *et al*[3] in a study of 1129 enuretic children have shown an annual spontaneous cure rate of approximately 15% for 5 to 18 year olds. For the affected child and family however, it can be a significant problem and indeed several studies have shown a deleterious effect on self-esteem, behaviour and quality of life[12,13,14]. Other far-

Table II: Inclusion Criteria for Data Analysis

1) Referrals seen from August 2003
2) Age 6 –18 years
3) only children with Primary NE
4) baseline wetting frequency of ≥ 6 WN /14
5) completing 12 weeks therapy by February 2006
6) completing a 2-week washout record (for DDAVP group only)

Table III: Demographic variables of study population

Variable	Study population n = 71(%)	Fluid Management and Reward System group n =23 (%)	DDAVP group n =48 (%)
Age in years			
6 - 8	23 (32.4)	6 (26.1)	17 (35.4)
9 - 11	33 (46.5)	11 (47.8)	22 (45.8)
12 - 14	12 (16.9)	6 (26.1)	6 (12.5)
15 - 18	3 (4.2)	0	3 (6.3)
Mean	*9.84*	*9.87*	*9.73*
Sex			
Males	34 (47.9)	14 (60.9)	20 (41.7)
Females	37 (52.1)	9 (39.1)	28 (58.3)
Ethnic Group			
Malay	23 (32.4)	9 (39.1)	14 (29.2)
Chinese	34 (47.9)	12 (52.2)	22 (45.8)
Indian	14 (19.7)	2 (8.7)	12 (25.0)
Family History			
Positive	27 (38.0)	7 (30.4)	20 (41.7)
Negative	40 (56.3)	16 (69.6)	24 (50.0)
Not known	4 (5.6)	0 (0)	4 (8.3)
Baseline Wetting (WN/14)			
6	8 (11.3)	3 (13.0)	5 (10.4)
7	3 (4.2)	3 (13.0)	0 (0)
8	6 (8.5)	3 (13.0)	3 (6.3)
9	2 (2.8)	1 (4.3)	1 (2.1)
10	5 (7.0)	1 (4.3)	4 (8.3)
11	3 (4.2)	1 (4.3)	2 (4.2)
12	3 (4.2)	1 (4.3)	2 (4.2)
13	3 (4.2)	0 (0)	3 (6.3)
14	38 (53.5)	10 (43.4)	28 (58.3)
Mean	*11.62*	*10.65*	*12.08*

Table IV: Results of Treatment (mean no. of WN/14)

Patient group	Baseline	During treatment	mean difference	p*	95 % confidence interval
All (n=71)	11.62	3.14	8.48	<0.001	7.37 - 9.59
FM +RS n = 23	10.65	1.87	8.78	<0.001	7.38 – 10.19
DDAVP n = 48	12.08	3.75	8.33	<0.001	6.80 – 9.86
DDAVP n = 48	12.08	wash-out 7.90	4.19	<0.001	2.80 –5.57

p* value using paired samples 2 tail t-test

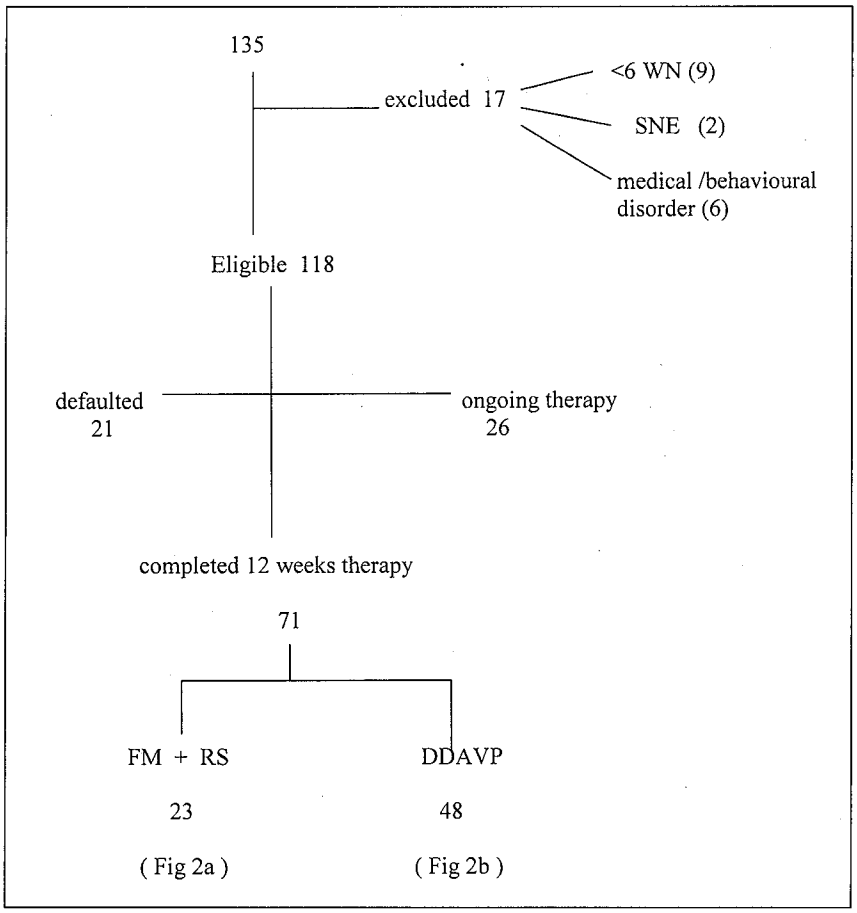

Fig 1: Study Design and Referrals seen between August 2003 and February 2006

Abbreviations: FM = fluid management
RS = reward system
DDAVP = desmopressin
WN = no. of wet nights

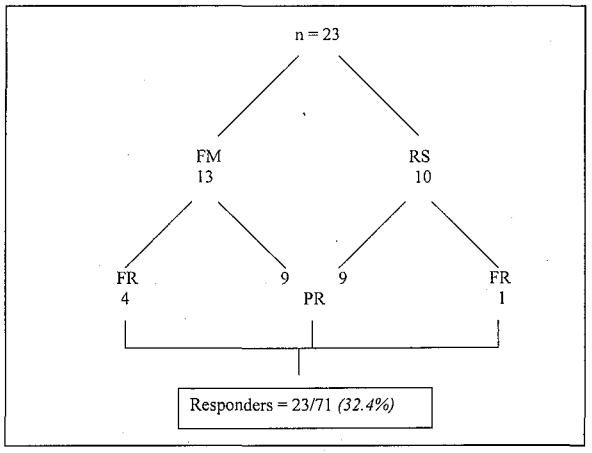

Fig 2: Outcome of Non-Pharmacological Treatment

Abbreviations: FM = fluid management;
RS = reward system
FR = full response

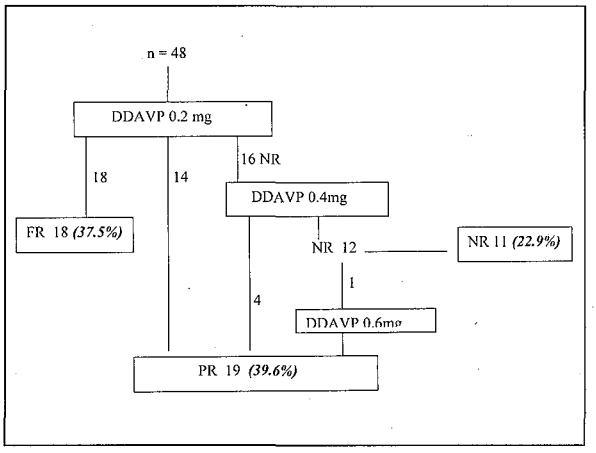

Fig 2b: Outcome of DDAVP Group

Abbreviations: FR =full response
PR = partial response
NR = no response

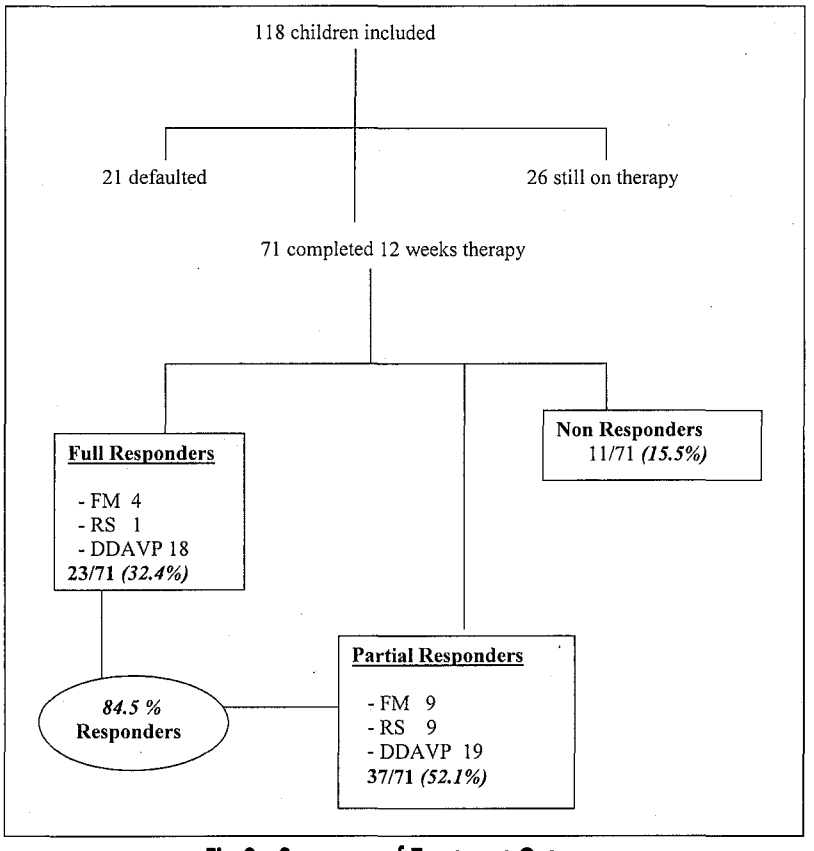

Fig 3: Summary of Treatment Outcomes

reaching consequences reported in the literature include under achieving at school, reluctance to go on a holiday or sleep-overs and loss of confidence in parenting skills[15,16]. The evidence that Malaysian parents also experience feelings of anxiety, guilt, embarrassment and frustration[11] prompted the need to assess treatment modalities and outcomes among Malaysian enuretic children.

To date, very few paediatricians in Malaysia have been treating NE, instead only offering therapy for short trips and holidays. With urbanisation and improvement in the socio-economic status of Malaysian families, issues such as bedwetting are becoming less acceptable and hence there is a need to determine if treatment of these children can be effective.

Children above the age of six were enrolled in this study because this is the age at which Malaysian children enrol into formal education and by age 8 or 9 years, school camps become a part of their extra-curricular activities. Table III shows that almost half of the children attending the clinic were in fact in the age bracket of 9 to 11 years. The higher number of Chinese referred for therapy compared to Malays or Indians, perhaps portrays the differences in cultural acceptance of bedwetting between the three races.

Many studies on the results of treatment of NE have been reported over the last ten years. Most use the same definition of partial response as in this study however, the majority of reports take full response as achieving 90 percent reduction in wet nights[17,18,19]. In this study however, FR was defined more stringently as zero wet nights or the child having achieved complete dryness. The reason for this difference is firstly, because the majority of the parents attending the clinic were expecting this outcome and secondly, the author believes that in treating a non life-threatening problem such as bedwetting, the clinical significance of achieving dryness as the outcome measure was more important than simply achieving a statistically significant reduction in wetting frequency.

The overall baseline mean number of wet nights as well as the baseline mean for the two treatment groups were between 10 to 12 nights per 14 nights. The therapy offered whether pharmacological or non-pharmacological, showed a statistically significant difference in the number of wet nights during therapy as shown in Table IV. The results also indicate that although the frequency of wet nights increased when DDAVP was discontinued during the two week wash-out interval, it was still significantly less than at baseline.

These results indicate that simple measures such as judicious management of fluid intake and simple reward systems may be all that is required in up to 32.4% of Malaysian bedwetters. Of those requiring further therapy, oral DDAVP can achieve 77% response and in particular, at least half of these children can be completely dry whilst on therapy. A total of 84.5% of all the children who continued with their chosen form of therapy had at least a 50% reduction in their frequency of wet nights. It must be noted that though the data was collected prospectively, cases enrolled were self-selected as only those who have come forward by referral to the clinic were studied. This in itself ensures the motivational level of the child and family and may have influenced the favourable outcome.

Of note also, is the fact that 21 of the 118 eligible families had defaulted after the first clinic visit. Perhaps these parents only wanted the reassurance that there was no organic pathology causing their child's bedwetting. Unfortunately, these parents could not be reached to confirm or refute this possible explanation.

In conclusion, childhood primary NE exists in Malaysia to the same extent as it does elsewhere in the world and these children and their parents have the same emotional anxieties reported in studies from other countries. Treatment of these enuretic children, both by simple measures and with oral DDAVP is effective and well tolerated. Significant reduction in the number of wet nights can be achieved in up to 84.5% of Malaysian children. Because more Malaysian parents are coming forward to seek therapy for a once socially and culturally acceptable problem, more paediatricians should be made aware of the favourable outcome of therapy in these enuretic children.

Future studies should evaluate the acceptance and effectiveness of other proven therapies such as the bedwetting alarm system and anti-cholinergic antidepressant agents in the Malaysian context. Furthermore, long term results of all these treatment modalities need to be assessed and their costs factored into the health care system in Malaysia.

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