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Daytime urotherapy in nocturnal enuresis: a randomised, controlled trial

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ABSTRACT

Objective According to international guidelines, children with enuresis are recommended urotherapy, or basic bladder advice, before treatment with evidence-based alternatives such as the enuresis alarm is given. The efficacy of this strategy has, however, not been supported by controlled studies. We wanted to test if basic bladder advice is useful in enuresis.

Design Randomised, controlled trial.

Setting Paediatric outpatient ward, regional hospital.

Patients Treatment-naïve enuretic children aged ≥6 years, with no daytime incontinence.

Interventions Three groups, each during 8 weeks: (A) basic bladder advice—that is, voiding and drinking according to a strict schedule and instructions regarding toilet posture, (B) enuresis alarm therapy and (C) no treatment (control group).

Main outcome measures Reduction in enuresis frequency during week 7–8 compared with baseline.

Results The median number of wet nights out of 14 before and at the end of treatment were in group A (n=20) 12.5 and 11.5 (p=0.44), in group B (n=22) 11.0 and 3.5 (p<0.001) and in group C (n=18) 12.5 and 12.0 (p=0.55). The difference in reduction of enuresis frequency between the groups was highly significant (p=0.002), but no difference was found between basic bladder advice and controls.

Conclusions Urotherapy, or basic bladder advice, is ineffective as a first-line treatment of nocturnal enuresis. Enuretic children who are old enough to be bothered by their condition should be offered treatment with the alarm or desmopressin.

Trial registration number NCT03812094.

What is already known on this topic?

⇒ Urotherapy, or basic bladder advice, is recommended as a first-line therapy against enuresis, but this recommendation is not based on prospective, controlled trials.

What this study adds?

⇒ Urotherapy was found to be no better than no treatment and clearly inferior to alarm therapy.
⇒ The treatment recommendations for enuresis should be changed.

INTRODUCTION

Approximately 1 in 10 children in early school age suffer from enuresis, and 3% of teenagers are still not dry at night.[1 2] Enuretic children have lower self-esteem and worse quality of life than their dry peers.[3 4]

Three pathogenic mechanisms are crucial in enuresis: nocturnal polyuria, high arousal thresholds and detrusor overactivity (DO).[5] The role of the latter mechanism is supported by the large overlap between enuresis and daytime incontinence[1 6] and the fact that anticholinergics may make the children dry at night.[7] Finally, DO has been observed by ambulatory cystometry in enuretic children.[8]

Most enuretic children do not need invasive evaluation, but a voiding chart is recommended as a crucial part of the investigation. In this way, it is assumed that prognostic information is gained.[9 10]

The primary treatment of enuresis, as reflected by global guidelines, rests on three pillars. The recommended first step is (1) bladder advice, or basic urotherapy. The next step is either (2) the antidiuretic drug desmopressin or (3) the enuresis alarm.[11 12] Of these alternatives, the enuresis alarm is the only one with clear curative potential.[13 14]

Urotherapy is defined as conservative, non-pharmacological, non-surgical treatment of the lower urinary tract (LUT).[10] The purpose of urotherapy is to educate the child about normal LUT function and to empower rehabilitation via behavioural modification. The underlying idea is that the child in this way is taught to more actively take command over their LUT function.[15] The cornerstones of standard urotherapy, as advocated for children with incontinence or enuresis, are the following:[15]

- education/demystification; explanation about normal LUT function and how the particular child deviates from normal,
- regular voiding habits according to a schedule, with micturition approximately every second hour and just before going to bed,
- regular drinking habits, with fluid intake spread evenly during the day and avoidance of excess fluid intake in the evenings,
- correct voiding posture, squatting with support for the thighs and feet,
- documentation of symptoms and voiding habits via repeated completion of voiding diaries,
- regular support, encouragement and feedback from the healthcare provider.

To emphasise that we do not here refer to more advanced urotherapy with components such as

cognitive behavioural therapy or biofeedback we have chosen to call the treatment basic bladder advice (BBA).

The rationale behind the recommendation of urotherapy or BBA as a first-line therapy in enuresis is that BBA is the cornerstone of treatment of daytime incontinence.[16] The tacit assumption is that by influencing LUT function during the day nocturnal bladder function will also normalise.

The problem here is a glaring lack of evidence. We recently performed the first randomised, controlled study of BBA in enuretic children and found no effect.[17] But these results need to be further explored. Furthermore, during our previous study the therapy was given during 4 weeks only.

Thus, the purpose of the present study was to provide more evidence for the efficacy, or non-efficacy, of BBA in enuresis by prolonging therapy to 8 weeks, and, crucially, including a non-treatment arm in the randomised study.

METHODS

Subjects

All enuretic children aged 6–11 years who were referred to the paediatric outpatient ward were invited to participate in the study, which was conducted at a regional paediatric clinic. Exclusion criteria were:

- present daytime incontinence,
- previous urotherapy,
- previous treatment with the enuresis alarm or second-line antienuretic therapy,
- voiding dysfunction or suspected LUT malformation,
- concomittant disorders influencing renal or LUT function,
- inability to give informed consent or comply with instructions given.

The enuresis of the participants need not be strictly monosymptomatic as long as the children had no daytime incontinence. We did this in order to include all enuretic children who would usually be considered appropriate candidates for BBA.

Baseline evaluation

At the initial visit to the study nurse, a detailed history was taken and a non-invasive urodynamic examination—that is, uroflow and residual urine assessment—was undertaken. The horizontal rectal diameter was assessed ultrasonographically. The nurse then supplied the family with a voiding chart and bladder diary to be completed at home. The following data were gathered:[10]

- nights with enuresis during 2 weeks,
- voided volumes at each voiding during 2 days,
- enuresis urine volume, by weighing of diapers, during three nights.

The children were then reassessed. Parents of children fulfilling the inclusion criteria gave written informed consent. If the child was considered constipated, either due to positive Rome IV criteria[18] or a rectal diameter of >30 mm,[19] laxative therapy was started according to international guidelines,[20] and the enuresis frequency was reassessed after 2 weeks.

The intervention

All children who completed the baseline investigations and still suffered from enuresis—including those who had been given treatment for constipation but did not become dry—were invited to take part in the randomised study. They were randomly consigned into three groups as described below (the randomised allocation was generated using the virtual sealed envelope service of Random.org in blocks of 3 and 6 and was blinded to everyone involved until the allocation was revealed by the study nurse to the individual family).

- Group A. BBA was given in accordance with international guidelines, as described above.[11] The treatment was given during 8 weeks by a qualified paediatric nurse and urotherapist. Contact by phone was made after 2 and 6 weeks.
- Group B. Alarm therapy was given in accordance with international guidelines.[9] The treatment was given during 8 weeks by a qualified paediatric nurse and urotherapist. Contact by phone was made after 2 and 6 weeks.
- Group C; controls. No active treatment was given to these children.

In all groups, wet nights were again documented during week 7 and 8. Regardless of group, all children were given information about LUT function and enuresis pathogenesis, and all ongoing laxative therapy was continued.

The study was conducted in accordance with the Helsinki Declaration and approved by the Regional Ethics Authority (Dnr 2018/004). Before the inclusion of patients was started, July 2019, the study protocol was registered at ClinicalTrials.gov ID: NCT03812094.

Statistics

The primary outcome measure was therapy response, defined as the reduction of the number of wet nights during the 2 weeks at the end of therapy (or no treatment), compared with before the intervention. The therapy response in the three groups were compared using between-subjects ANOVA or Kruskal-Wallis tests. The response to therapy—response, partial response, non-response—according to the International Children's Continence Society (ICCS) classification[10] was also noted.

Possible predictive factors influencing therapy response were explored among all data gathered at baseline using t-tests, Mann-Whitney tests or χ^2 tests depending on the type and distribution of the variables.

In order not to miss a true difference in therapy response of three wet nights in 2 weeks (a smaller difference than that would not be clinically relevant) at least 15 children were needed in each treatment group. We assumed that some children would drop out and thus planned for inclusion of 20 patients in each group. The power calculations arriving at this number are based on the enuresis frequency of comparable populations used in our previous research.[17 21]

RESULTS

Study population

Recruitment started July 2019 and finished January 2021. Ninety-eight children were invited to participate, 25 of whom declined due to various reasons. After the first visit to the nurse, a further seven children dropped out from the study, either because the child spontaneously became dry (n=3) or due to failure to return the bladder diary and voiding chart. One child who was found to be constipated became dry by addressing the bowel problem and three more children dropped out before randomisation, leaving 62 children. After randomisation, two families in the control group chose to drop out since they were unmotivated to complete the voiding chart and bladder diary without active therapy. No child dropped out from any of the active treatment arms.

Thus, 60 children completed the full study: 20, 22 and 18 in the BBA, alarm and control groups, respectively. The age and sex distribution of the dropouts did not differ from those of the children completing the study.

Table 1 History and voiding chart data, at baseline, comparison between study groups

	BBA (n=20)	Alarm (n=22)	Controls (n=18)	P value
Heredity (parents or siblings)	12/20 (60%)	10/22 (46%)	6/18 (33%)	0.26
Urgency	16/20 (80%)	15/22 (68%)	10/18 (56%)	0.27
Previous daytime incontinence	7/20 (35%)	11/22 (50%)	12/18 (67%)	0.15
High arousal thresholds	16/20 (80%)	21/22 (96%)	16/18 (89%)	0.30
Constipation	8/20 (40%)	3/22 (14%)	8/18 (44%)	0.07
Wet nights per 2 weeks before intervention	10.3±4.6	9.7±4.1	10.4±4.4	0.86
Daytime micturition frequency	3.5±5.4	5.7±1.5	5.5±2.6	0.87
Enuresis volume*	65±37	71±72	72±36	0.91
Urine production per 24 hours/kg	30±13	28±12	27±11	0.80
Nocturnal urine production, wet nights*	109±51	118±72	121±48	0.85
Maximum voided volume, morning void excluded*	76±35	74±29	84±31	0.58
Maximum voided volume, morning void included*	82±34	85±37	92±26	0.63
Average voided volume, morning void excluded*	51±25	44±16	47±16	0.53
Average voided volume, morning void included	50±22	47±16	49±14	0.85

Data shown are either proportions (%) r, mean±1 SD.
*All volumes expressed as percentages of expected bladder capacity for the child's age, according to the Koff-Hjälmås formula.[27]
BBA, basic bladder advice .

There were 44 boys and 16 girls completing the study. Their age was 6–10 years (mean 7.2, 1 SD=1.3 years) and their body mass index was 13.8–24.8 kg/m^2 (mean 16.7, 1 SD=2.2 kg/m^2). The sex, age and body mass index distribution did not differ between the three treatment arms (data not shown).

In table 1, baseline history data and voiding chart data for the three groups are compared. As can be seen, there were no significant differences between the groups. Some families were unable to provide full data for all the variables.

Antienuretic effect

The median number of wet nights (with range) per 2 weeks before the intervention was 12.5 (1.0–14), 11.0 (1.2–14) and 12.5 (1.0–14) for the BBA, enuresis alarm and control groups, respectively. The corresponding figures for week 7 and 8 in the study period were 11.5 (0–14), 3.5 (0–13) and 12 (0–14). Looking at the reduction of wet nights between the two time points the corresponding figures were 0 (–4.9 to 7.9), 4.5 (0 to 13.9) and 0 (–4 to 0.3) or, expressed as positive percentages, 0 (0–100)%, 47 (0–100)% and 0 (0–34)%. This is illustrated graphically in figure 1. As can be seen, only the alarm significantly reduced the number of wet nights, the p values for the BBA, alarm and control groups being 0.44,<0.001 and 0.55, respectively.

When the absolute and percentual reduction of wet nights in the three study groups were compared, the difference between them came out highly statistically significant (p<0.001 and p=0.002, respectively). When making pairwise comparisons, with Bonferroni corrections, there was no significant difference between BBA and the control group (p=1), whereas the alarm significantly differed from both BBA (p=0.016) and no treatment (p=0.004).

The proportion of full responders, intermediate responders and non-responders, according to the ICCS terminology,[10] was 10%, 5% and 85% for the BBA group, 27%, 23% and 50% for the alarm group and 11%, 11% and 78% for the control group.

The situation for the children in the BBA arm is highlighted in figure 2. Although the number of children becoming dry during BBA (n=2) was too small for proper evaluation, it should be noted that these children had a baseline enuresis frequency of less than 50% of the nights. Possible predictors for therapy response among the baseline variables (ie, the same variables as are shown in table 1) were explored comparing responders and non-responders within all three groups, but none came out statistically significant (data not shown).

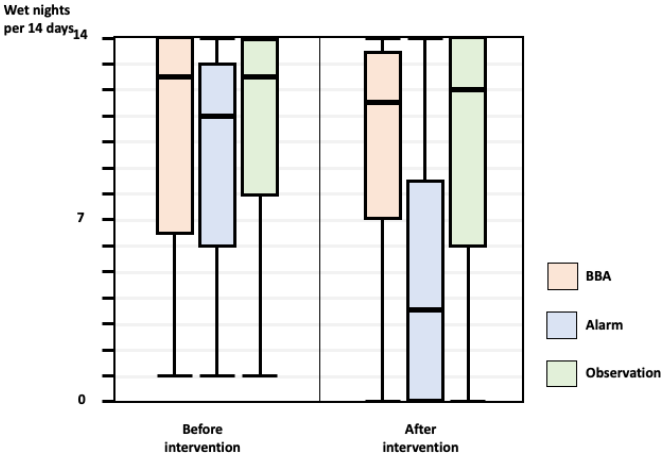

Figure 1 Wet nights before and after the intervention. BBA, basic bladder advice.

DISCUSSION

We have performed the first prospective, randomised study comparing the efficacy of BBA with the enuresis alarm or no treatment, in children with nocturnal enuresis without daytime incontinence. We found BBA to be equally effective as no treatment and inferior to the alarm.

Previous studies on BBA in enuresis have either been retrospective, uncontrolled or both. In a retrospective, uncontrolled evaluation of 22 children attending a tertiary clinic in Gothenburg, Sweden, enuresis frequency was found to decrease in all children, but 10 of them were also given alarm therapy or desmopressin.[22] Robson and Leung evaluated 1 month of urotherapy in 40 children, 23 of whom dropped out of treatment. Of the minority who completed the trial 22% became dry. There were no controls.[23] Pennesi *et al* evaluated urotherapy in 250 enuretic children at a specialist clinic. Treatment made 60% dry and 11%

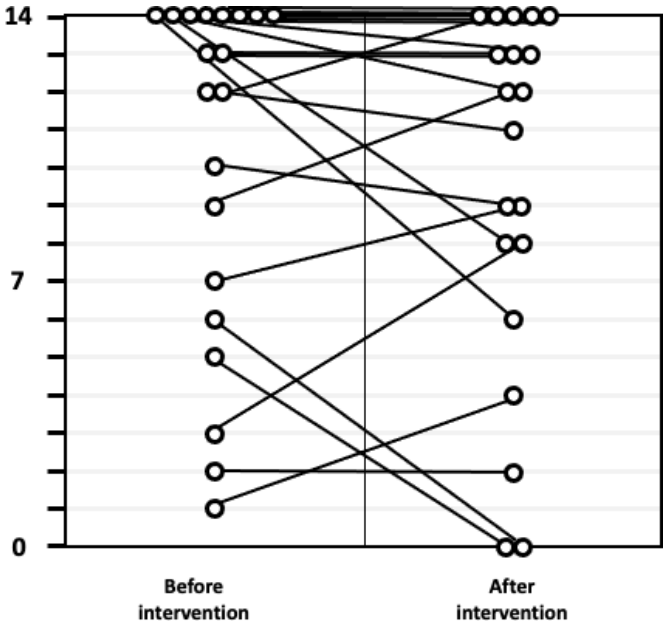

Figure 2 Wet nights of individual subjects receiving basic bladder advice, before and after the intervention.

partially improved, but 26% of the children dropped out and there was no control group.[24] In a Belgian, uncontrolled study of 41 children who were trained for 5 months only 14% of the children became dry.[25] Finally, the team in Gdansk, Poland, evaluated BBA given to 43 previously untreated children. The effects were modest: after 3 months of therapy only 18% become dry. Again, there was no control group.[26]

In contrast to these studies, our study has the benefits of being prospective, randomised, controlled and performed on treatment-naïve enuretic children. Although we cannot be sure that our study population is fully representative to the enuretic population at large we do believe that we, by recruiting families who sought help via an ordinary outpatient ward, and subjecting the children to a minimum of examinations, came closer than previous studies. The treatment was given by an experienced specialist nurse, who meticulously instructed the children and guardians. Furthermore, we made reasonably sure that bowel problems was not a cause behind treatment failure.

Only two children became dry during BBA. They had a lower baseline enuresis frequency than the many non-responders. Two patients in the control group became dry as well, as did three before even being randomised into a treatment group. We suspect that this was a placebo effect and/or that these children were about to become dry anyway.

A potential drawback is that we do not actually know for sure that the instructions given were followed by the families. All participating families were given voiding diaries to complete and were encouraged with repeated contacts by the nurse. Still, we cannot be sure that the families were 100% adherent. But more direct verification of the adherence would constitute an intervention in and by itself and would diminish the clinical relevance of our findings. We wanted to evaluate BBA as it can reasonably be applied in the real world.

It needs to be underlined that urotherapy also includes practices that should be part of all good nursing and good doctoring, such as explanation and demystification, removal of guilt and the establishment of a trusting relationship between the family and the healthcare provider. We certainly do not wish to question the value of this. But obviously something more is needed to make the child dry.

Why was not BBA effective? We see two possible, non-exclusive, explanations.

First, as mentioned above, the families may not have followed our instructions. But if they did not in this situation, they will not do so in the ordinary clinical setting either. And if the instructions and follow-up of the nurse had been even more intense the therapy given would surely be much too labour-intensive to qualify as a first-line therapy of enuretic children in primary care. A second, more plausible explanation is that to train the bladder during the day may have only limited effect on bladder function during the night.[17]

It could be argued that the children may have become dry if therapy was prolonged beyond 8 weeks. This may certainly be the case, but this would in our view disqualify the therapy as a first-line choice anyway. Another relevant issue here is that if we had prolonged therapy to, say, 12 weeks, more families in the BBA or control groups would probably have dropped out.

In fact, we find it surprising that BBA is routinely recommended as a first-line antienuretic therapy, given the lack of evidence for its efficacy. This way valuable time is taken from a scarce and qualified resource, that is, the urotherapists, and effective treatment for the affected children is delayed.

CONCLUSION

Urotherapy, or BBA, is ineffective as a first-line treatment of nocturnal enuresis. Enuretic children who are old enough to be bothered by their condition should be offered treatment with the alarm or desmopressin.

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Contributors MB conceptualised and designed the study, recruited study patients, collected and analysed the data, drafted the initial manuscript and reviewed and revised the manuscript. AB collected and analysed the data, drafted the initial manuscript and reviewed and revised the manuscript. BHS, MT and TN conceptualised and designed the study, supervised data collection and analysis and actively participated in the production of the manuscript at all stages. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. TN is the guarantor of the work

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Competing interests None declared.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Anonymised data may be provided on reasonable request.

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