
Do Holding Exercises or Antimuscarinics Increase Maximum Voided Volume in Monosymptomatic Nocturnal Enuresis? A Randomized Controlled Trial in Children

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Purpose: We assessed prospectively the efficacy of holding exercises and/or antimuscarinics (oxybutynin chloride and placebo) for increasing maximum voided volume in prepubertal children with monosymptomatic nocturnal enuresis.

Materials and Methods: We randomly allocated 149 children to 5 groups, namely holding exercises with placebo (group A), holding exercises with oxybutynin (group B), placebo alone (group C), oxybutynin alone (group D) and alarm treatment (controls, group E). Maximum voided volume was the greatest voided volume from a 48-hour bladder diary, and holding exercise volume was the greatest volume produced with postponement of voiding after a fluid load, once daily for 4 days. Study medication, holding exercise procedures and alarm treatment were administered for 12 weeks.

Results: Holding exercises combined with placebo or oxybutynin significantly increased holding exercise volume and maximum voided volume, by 25% ($p < 0.001$) and 21% ($p < 0.01$), respectively, in group A, and by 43% ($p < 0.001$) and 41% ($p < 0.001$), respectively, in group B. Medication without holding exercises (groups C and D) did not increase holding exercise volume or maximum voided volume, and in these groups oxybutynin was not significantly superior to placebo. A borderline increase in holding exercise volume did not affect maximum voided volume in group E. Monosymptomatic nocturnal enuresis response was significantly lower with all 4 holding exercise volume modulating treatments (7%) compared to alarm therapy (73%).

Conclusions: In the treatment of children with monosymptomatic nocturnal enuresis maximum voided volume can be increased significantly through holding exercises, but not with oxybutynin chloride alone. Compared to controls, increasing maximum voided volume had a minimal effect on monosymptomatic nocturnal enuresis.

Key Words: nocturnal enuresis, urinary incontinence, oxybutynin, behavior therapy

The pathophysiology of MNE remains poorly understood. However, the balance between nocturnal urine output and bladder capacity (MVV) is considered important, and this principle has generated 2 strategies for treatment—decreasing nocturnal urine output and/or increasing bladder capacity.¹⁻⁴ Functional bladder capacity is defined in adults⁵ and children^{6,7} as MVV on a 48-hour frequency-volume chart. However, normal values for children are absent. Judging MVV as small for age is done with either a recently adapted linear function for CBC and age,⁷ or with the full 5% to 95% range of CBC for age.⁸

Based on the assumption that detrusor overactivity causes small for age bladder capacity in MNE, many studies use antimuscarinics to increase bladder capacity.⁹⁻¹¹ Another time-honored method to increase bladder capacity consists of holding exercises, in which urine output is increased with a standardized water load, and at each urge to void the subject has to postpone voiding for as long as possible.¹²⁻¹⁴

Combinations of these 2 methods have also been reported.^{15,16} Most of these studies are retrospective and claim either a significant immediate response of MNE or a better cure rate with subsequent treatment of MNE. The reported increase in bladder capacity varies considerably, depending on the parameter chosen. In many studies bladder capacity is expressed as the maximum holding exercise volume. Indeed, functional bladder capacity (MVV) is difficult to assess in MNE. It often results from the first void in the morning, which will be small when a child wets the bed. To find a maximum, volumes voided and bedwetting volumes have to be measured during a period of 48 hours.¹⁷

The lack of evidence for the widespread use of antimuscarinics and holding exercises in MNE prompted us to design a randomized controlled trial comparing interventions in 4 groups of children with MNE, namely treatment with oxybutynin chloride or placebo alone or in combination with a 4 days per week regimen of standardized fluid intake and holding exercises. A 5th group, to be treated with alarm only, was planned as a control. First, we wanted to find the most effective way to increase HEVs significantly, by comparing the 4 interventions. Then, we assessed how increased HEV affects MVV for age in children with MNE. We also wanted to know the response of MNE to increased MVV, by

Submitted for publication March 30, 2007.

Study received medical ethics committees approval.

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comparing the 4 intervention groups with the control group. In the 2nd part of this trial the 4 groups pretreated to increase MVV will subsequently receive alarm treatment, and response and cure rates of this treatment will be reported separately.

PATIENTS AND METHODS

The definitions for parameters and conditions in this study comply with the guidelines of the 2nd standardization report for lower urinary tract function in children and adolescents, published recently on behalf of the International Children's Continence Society.⁷

Patients

A total of 204 prepubertal patients older than 5 years referred to our institutions between June 2003 and January 2005 were considered eligible for this study. Informed consent was obtained in writing, including consent regarding possible side effects of the study medication, from a parent or legal guardian for every participant. Standardized medical history, complete physical examination and uroflow study with post-void residual allowed us to exclude anatomical or functional incontinence. The inclusion criterion was a record of at least 14 wet nights in the 4 weeks before randomization. Exclusion criteria were previous treatment with alarm, desmopressin or anticholinergics completed less than 3 months before start of the study, age younger than 5 years at randomization and puberty beyond Tanner stage 1.

Randomization

Randomization was stratified for participating hospital, patient sex and age, Tanner stage, family history of MNE, previous treatment and bladder capacity class. Patients had a 4 out of 5 chance of being allocated to 1 of the 12-week treatment groups, with the aim of increasing HEV, namely holding exercises with placebo (group A), holding exercises with oxybutynin (group B), placebo alone (group C) and oxybutynin alone (group D). A 5th of the patients were allocated to a control group (E) for 12 weeks of alarm therapy. Allocation took place after a 3-week run in period (see table).

Baseline Evaluation: Maximum Voided Volume and Holding Exercise Volume

At entry a 48-hour frequency-volume chart was used to determine the largest voided volume at home without specific instructions as to fluid intake. To measure bedwetting volumes, children wore pre-weighed diapers (Tena®Pants Plus, with a

sensor for a remote enuresis alarm (Elther®) alerting only the parents.¹⁷ The largest voiding on the 48-hour chart was taken as MVV. Children then performed a holding exercise. An oral water load of 20 ml/kg body weight was administered spanning 30 minutes, and voiding was postponed for as long as possible. Voided volume was then noted.

This procedure was performed for 4 consecutive days, and the largest volume was noted as HEV. The same procedure has been used as intervention. The largest of the 2 volumes, MVV or HEV, was corrected for body surface area and used to determine bladder capacity class for randomization. Volume less than 180 ml/m² was classified as small, while volume 180 ml/m² or greater was classified as normal.

Interventions: Holding Exercise Procedure and Study Medication

All patients were instructed to adhere to a normal, regular fluid intake and voiding regimen, and to note the wet and dry nights in a diary during the 12 weeks of treatment. The table outlines the time frame, in weeks, for the study. Holding exercises were to be done 4 days per week during the 12 weeks of treatment, and the resulting volumes were measured and plotted at home, providing a graphic record. Study medication was to be administered twice daily, at 4:00 pm and immediately before bedtime, in the form of a clear liquid, at 0.4 ml/kg body weight per day. Oxybutynin chloride was supplied as 1 mg/ml Ditropan®, and placebo solution was produced by the pharmacy of the participating university hospital. Study medication was dispensed by the university pharmacy in numbered bottles, and attending physicians and patients were blinded to the medication. Two visits to assess safety and compliance were scheduled, at treatment weeks 4 and 8, and empty bottles were returned and checked at treatment weeks 4, 8 and 12.

Primary Outcome: Holding Exercise Volume and Full Response

A 2nd evaluation of baseline parameters was done immediately after the treatment period, to assess changes in HEV and MVV. At the same time the frequency of wet nights was reassessed, and wetting 1 night or less during the last 28 consecutive days was considered a full response of MNE to treatment.⁷

Statistical Methods

Holding exercise volumes are presented as box plots separately for all 5 groups and for treatment weeks 0 and 12. Statistical testing of differences of HEV and MVV after

Time table for randomized controlled trial of holding exercises with and without antimuscarinics

	Treatment Wk					
	T -4	T -1	T0	T4	T8	T12
Office visit	X		X	X	X	X
Uroflow (residual vol)	X			X		
History + physical examination	X					X
HEV and MVV assessment		X				X
Assessment of dry nights	X		X	X	X	X
Pretreatment (groups A, B, C, D)			X	X	X	X
Alarm treatment (group E)			X	X	X	X

Groups A and B performed holding exercises and received antimuscarinics, groups C and D received antimuscarinics alone, and group E (controls) received alarm therapy alone.

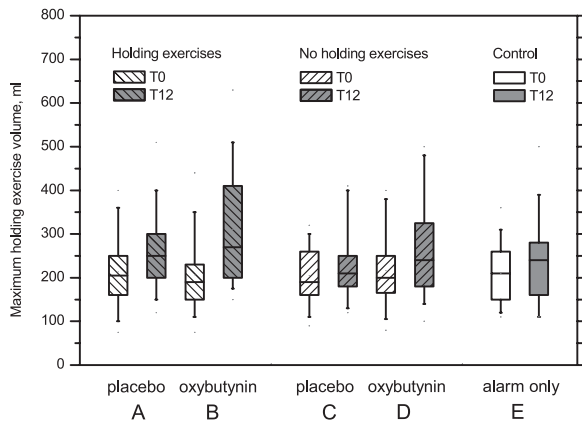


FIG. 1. Change in holding exercise volume before (T_0) and after (T_{12}) 12 weeks of HEV modulating treatment. Increase was statistically significant in groups performing holding exercises and receiving placebo or oxybutynin but not in groups receiving placebo or oxybutynin alone. Boxes with medians and quartiles, whiskers at 5% and 95%.

treatment was done by logarithmic transformation and repeated measures analyses of variances, with the factors “therapy” (oxybutynin, placebo), “holding exercises” (exercises, no exercises) and their interaction, and individual baseline for HEV as covariates. Scatter plots reveal the posttreatment shift for MVV for age, with and without holding exercises, in comparison to the 5% to 95% range of CBC for age and the recently published linear function $0.65(30x + 30)$ ml, where x is age in years.^{7,8} The rates of full response of MNE immediately after treatment (week 12) are given by percentage and 95% confidence intervals.

Statistical analyses of differences were done by multifactorial stepwise logistic regression, using “therapy” and “holding exercises” as factors, and HEV baseline, sex, age and treatment history as covariates. The level for assessment of statistical significance was predefined as $2\alpha = 0.05$ (2-sided). Resulting p values are given descriptively using Bonferroni’s rule for α -adjustment after multiple testing.

RESULTS

Of the 204 eligible children and families 45 refused informed consent. During the run in period 2 children became dry at night, 2 withdrew consent and 6 could not follow the protocol for other reasons. In all, 149 children were randomly allocated to the study treatment groups—108 boys and 41 girls ranging in age from 5.9 to 12.7 years (median 7.5). Of the patients 30% had been treated for MNE more than 3 months before the run in period. Medication side effects were limited, and included headache in 1 child in the oxybutynin plus holding exercises group, who consequently dropped out of the study. Seven more children dropped out because the effect of treatment was less than expected, including 1 in the oxybutynin group, 2 in the placebo group, 2 in the placebo plus holding exercises group and 2 in the control group.

Changes in Holding Exercise Volume

Figure 1 illustrates the changes in HEV for all 5 groups after 12 weeks of HEV modulating treatment, in box plots. With initial HEV values of 200 to 250 ml the changes can be expressed as the median of individual percentage in-

creases after treatment. In the 2 groups performing holding exercises HEV increased significantly when combined with placebo (group A, 25%, $p < 0.001$) and when combined with oxybutynin (group B, 43%, $p < 0.001$). In the 2 groups not performing holding exercises placebo (group C) increased HEV by 11% ($p > 0.1$) and oxybutynin (group D) increased HEV by 15% ($p = 0.054$). Statistically, these increases are not significant. In the controls (group E) HEV increased by 20% ($p = 0.048$), and statistically this increase borders on significance.

Changes in Maximum Voided Volume

The increase in HEV obtained with HEV modulating treatment was expected to have a lasting effect on MVV. Changes in MVV can be expressed as the median of individual percentage increases after treatment. Holding exercises with placebo (group A) increased MVV by 21% ($p < 0.01$), and holding exercises with oxybutynin (group B) increased MVV by 41% ($p < 0.001$). Placebo and oxybutynin without holding exercises had an insignificant effect on MVV, with a 4% increase for placebo ($p < 0.65$) and an 8% increase for oxybutynin ($p < 0.25$), similar to the 8% increase ($p < 0.65$) in the control group. Figure 2 illustrates that the effect of 12 weeks of HEV modulating treatment on individual MVVs versus age is slight but significant with holding exercises (groups A and B), and negligible without holding exercises (groups C and D). The increase in HEV after treatment in groups A and B translates into a significant shift in MVV for age. Group E, of which 73% had a full response to MNE, exhibited a significant increase in HEV ($p = 0.048$) but no change in MVV after alarm treatment.

Full Response of Nocturnal Enuresis

Figure 3 demonstrates the chances, with 5% to 95% confidence intervals, of having 1 wet night or less in the last 28 consecutive nights of the treatment period (full response of MNE) in all treatment groups. Compared to alarm treatment in the control group, all 4 HEV modulating treatments had a significantly decreased full response ($p < 0.001$). The differences in response between holding exercises plus placebo (group A), holding exercises plus oxybutynin (group B), placebo alone (group C) and oxybutynin alone (group D) are not statistically significant ($p > 0.22$). Multifactorial logistic regression tells us the factor “holding exercises” has no significant influence ($p > 0.75$) on the response rate of MNE, with the full response being 7% with or without holding exercises. The factor “therapy” also has no statistically significant influence on response rate ($p > 0.1$), although placebo (groups A and C) yielded a response rate of 2%, and oxybutynin (groups B and D) yielded a response rate of 12% ($p > 0.1$). Multifactorial logistic regression identified alarm treatment as the single factor defining full response of MNE. Starting values for HEV or MVV were not significantly related to response of MNE.

DISCUSSION

It is widely accepted that a small for age bladder capacity has a part in the pathophysiology of MNE.^{3,4,11,18} Despite the lack of prospective studies, anticholinergics and holding exercises aiming to increase bladder capacity have been

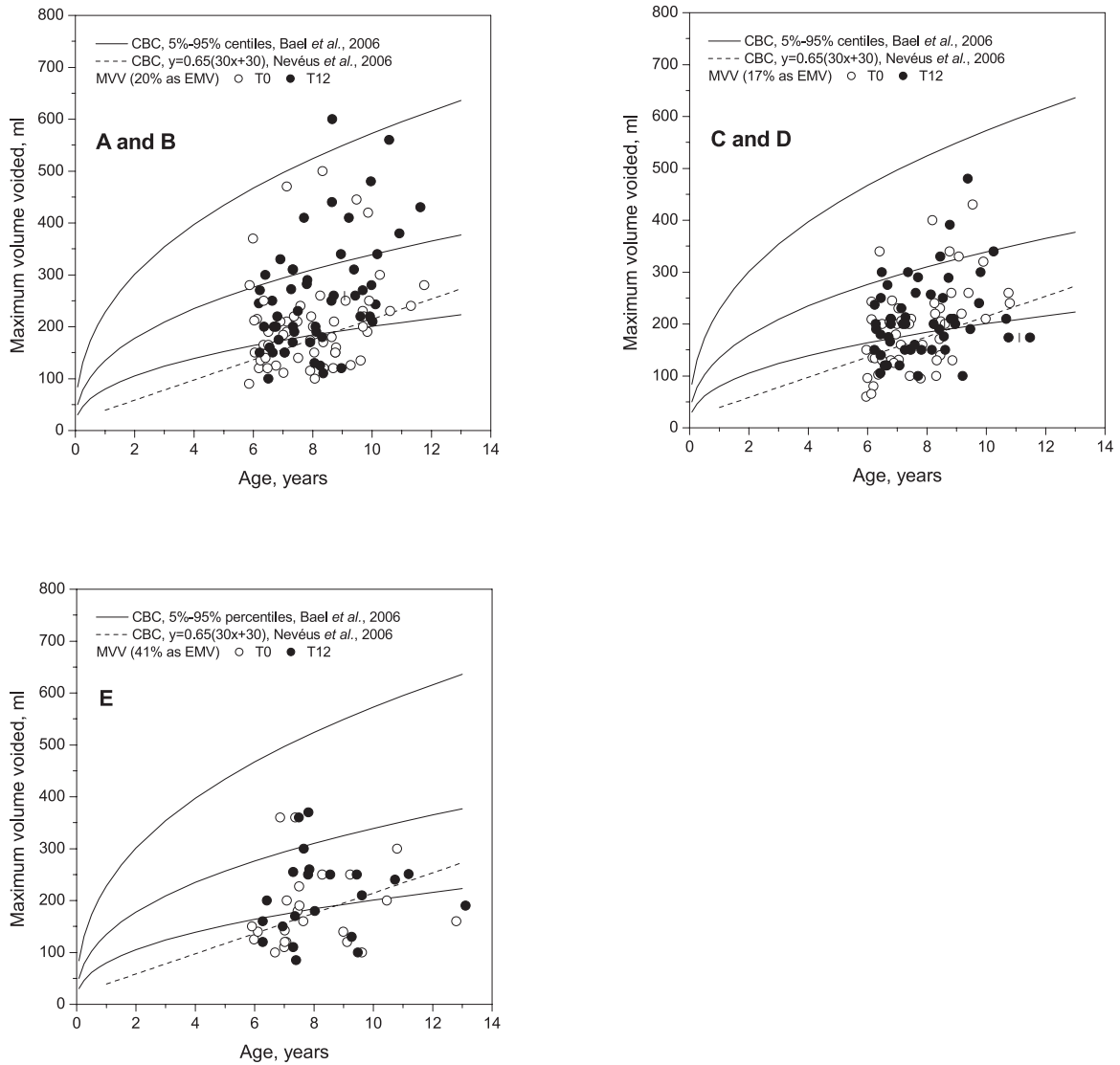


FIG. 2. Individual MVV before and after holding exercises with placebo or oxybutynin (*A and B*), before and after placebo or oxybutynin alone (*C and D*), and before and after alarm therapy (controls, *E*). Only groups *A and B* exhibit significant increase in MVV.

proposed as successful ways to treat MNE.^{9–12,15,16} Holding exercises are more effective in increasing HEV in children with MNE than oxybutynin or placebo alone, and the differ-

Treatment groups		Response rate		
Holding exercises	A placebo	1/29	3%	■
	B oxybutynin	3/30	10%	■
No holding exercises	C placebo	0/30	0%	■
	D oxybutynin	4/30	13%	■
Placebo	A + C	1/59	2%	■
Oxybutynin	B + D	7/60	12%	■
Alarm only	E control	22/30	73%	■

FIG. 3. Full response of MNE with 95% confidence intervals after 12 weeks of HEV modulating treatment, compared to 12 weeks of alarm treatment only. All groups or combinations have low response rates compared to controls. Difference in response rates between oxybutynin (*B + D*) and placebo (*A + C*) suggests oxybutynin is superior to placebo, although this difference is not statistically significant.

ence between oxybutynin and placebo is not statistically significant (*fig. 1*). To judge the effect of increased HEV on MVV, we plotted MVV for age separately for the groups treated with (*A and B*) and without holding exercises (*C and D*), referencing the plots with the 5% to 95% range for CBC and age, and with the recently published linear function $0.65(30x + 30)$ ml, where *x* is age in years (*fig. 2*).^{7,8} The 12 weeks of holding exercises had a significant effect on MVV, while oxybutynin and placebo had no effect on MVV. We also saw that a 20% increase in HEV did not affect MVV in the control group (group *E*) with successful treatment of MNE (73%).

Whatever the target for increasing bladder capacity, multifactorial logistic regression did not select HEV or MVV in our patients with MNE as related to a full treatment response of MNE. Thus, the extremely low response rate of HEV modulating pretreatment does not justify treatment of MNE with holding exercises and/or anticholinergics. The question of whether HEV and MVV are factors influencing relapse and cure rates of alarm therapy can only be answered by further prospective studies. In the 2nd part of this

trial groups A, B, C and D will subsequently receive alarm treatment, and response and cure rates of this treatment will be reported separately.

The reported success of oxybutynin in MNE comes mostly from observational studies. Where earlier studies claimed efficacy based on a partial response, or a full response in selected cases, we opted for a full response and intent to treat analysis. Studies on the effect of holding exercises on MNE have had similar shortcomings.^{15,16} In addition, the early observation by Starfield and Mellits¹² that exercise induced increase in bladder capacity improved bedwetting was not confirmed by later studies.¹³ The few controlled trials of oxybutynin for treatment of MNE have shown full response rates of 10% to 20%,⁹ which is similar to what we found.¹⁹ Our data suggest that oxybutynin is superior to placebo, measured by the full response rates of 2% and 12%, respectively, but this difference is not statistically significant ($p > 0.1$, fig. 3).

This study highlights the value and efficacy of alarm treatment. The 73% full response rate with alarm is similar to the response rates immediately after treatment found in other controlled trials.²⁰

In conclusion, small for age values for maximum voided volume (functional bladder capacity) in MNE can be remedied with holding exercises but with a negligible effect on the incidence of wet nights.

ACKNOWLEDGMENTS

Tena Pants Plus, Svenska Cellulosa Aktiebolaget, Stockholm, Sweden, provided the diapers used to measure bedwetting volumes reliably, and Elther, Weelde, Belgium, supplied valuable assistance with the remote bedwetting alarm. Sanofi Synthelabo Belgium supplied Ditropan solution.

Abbreviations and Acronyms

CBC	=	cystographic bladder capacity
HEV	=	holding exercise volume
MNE	=	monosymptomatic nocturnal enuresis
MVV	=	maximal voided volume

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