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TRANSURETHRAL INTRAVESICAL ELECTROTHERAPY FOR NEUROGENIC BLADDER DYSFUNCTION IN CHILDREN WITH MYELODYSPLASIA: A PROSPECTIVE, RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Myelomeningocele is the most common cause of neurogenic bladder dysfunction in children. Urinary incontinence is socially disabling for many of these children and undetected elevations in detrusor pressure can lead to serious upper tract damage. Sensory receptors in the bladder mucosa and submucosa provide afferent information to the central nervous system regulating the micturition reflex. Since 1959 Katona and several other investigators have used intravesical electrotherapy for diagnosis and treatment of the neuropathic bladder. Our objective was to conduct a randomized, sham controlled and blinded clinical study on the efficacy of transurethral intravesical electrotherapy in treating urinary incontinence in the myelodysplastic child.

A total of 36 children was enrolled in the study and 31 completed the entire protocol. Of the patients completing the study 13 were randomly selected to serve as an internal sham control having the electrocatheter placed without activating the stimulator. These patients were subsequently treated with a 3-week course of electrotherapy. The remaining 18 patients completing the study were randomly selected to undergo 2, 3-week courses of intravesical bladder stimulation. Urodynamic studies were performed before and after each treatment series. Detailed daily questionnaires were submitted to each participant covering subjective improvement in urinary continence and any development of bladder sensory awareness. Analysis of the urodynamic data and questionnaires failed to reveal any statistically significant increase in bladder capacity, development of detrusor contractions, improvement in detrusor compliance or the acquisition of bladder sensation allowing timely intermittent catheterization preventing urinary incontinence.

KEY WORDS: neural tubal defects, electric stimulation, bladder, urinary incontinence

The most common cause of neurogenic bladder dysfunction in children is myelodysplasia. While some of these children have urinary incontinence with an open bladder neck and detrusor areflexia, others have uninhibited detrusor contractions and poorly compliant bladders.[1] As many as 50% of these children are at risk for significant urinary tract damage if elevated bladder pressures go undetected and are not corrected.[2] Since 1984 intravesical transurethral bladder stimulation has been used in the United States as a diagnostic and rehabilitative technique for children with myelodysplasia.[3-6] Katona originally introduced intravesical bladder stimulation in 1959.[7] Worldwide, several other investigators have used intravesical bladder stimulation for the treatment of neurogenic bladder dysfunction secondary to a variety of factors, including spinal cord injury, myelodysplasia and other neurological diseases.[8-11] Impressive results of transurethral intravesical bladder stimulation have been reported, including the restoration of bladder sensation with filling and an urge to void, initiation of detrusor contractions, conscious urinary control and a significant increase in bladder capacity. In an effort to evaluate transurethral intravesical bladder stimulation in children with myelodysplasia, we designed a prospective, blinded, randomized clinical trial with partial cross-over, using an internal control population and periodic urodynamic evaluation to evaluate and quantify objectively changes with bladder stimulation.

MATERIALS AND METHODS

A total of 36 children with myelodysplasia seen regularly at the Texas Scottish Rite Hospital in Dallas was entered into the study. Parents of children with the motivation to follow an intensive outpatient treatment regimen were encouraged to participate. Of the 36 children 31 finished the protocol and were available for analysis. Children were randomly assigned to either sham or active treatment. According to the treatment algorithm 13 children were assigned to initial sham treatment, while 18 were assigned to active treatment (fig. 1). The initial treatment phase was 3 weeks with daily treatment sessions 5 days per week. This initial treatment phase was followed by a 3-month hiatus during which symptoms were monitored but no sham or active treatment was given. Following this interval the

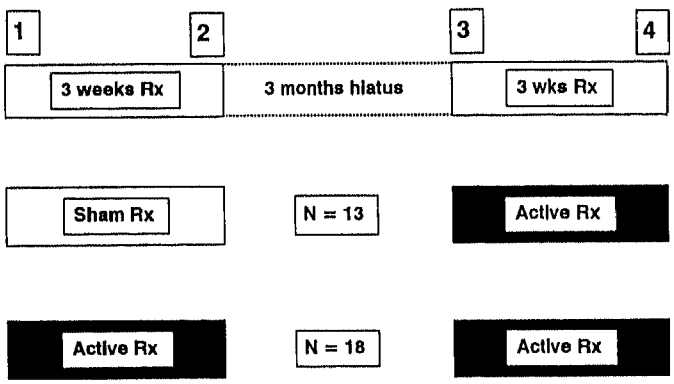

FIG. 1. Treatment algorithm illustrates stimulation protocol, number of patients in each group and intervals for urodynamic studies. *Rx*, treatment.

13 sham treated children underwent 3 weeks of active treatment, while the 18 previously treated patients were given active treatment for another 3 weeks (partial cross-over). This design was chosen because of ethical problems involved in offering sham treatment for 3 weeks to 1 group and actively treating the other group. The 13 patients enrolled in the true cross-over design were analyzed as a separate group. Comparisons were made between the cross-over and the twice treated group when applicable, and the initial urodynamic investigation data were analyzed for all 31 children who completed the protocol.

Evaluation and entry into the study included an extensive questionnaire and baseline urodynamic study measuring subtracted bladder pressure and capacity at a slow fill rate (normal saline at 10 ml./minute) with the patient in the supine position. Of the children 13 were entered into the sham arm, and 18 were entered into the treatment arm and were treated during both cycles. There were 12 boys and 19 girls between 6 and 12 years old (mean age 7.4 years). There were 4 low thoracic and 27 lumbosacral lesions, and 7 complete and 24 partial lesions. Twenty children (65%) were on clean intermittent catheterization and all but 1 were diaper dependent. Some bladder sensation (fullness) was present in 26% of the patients. Only 19% of the children had bowel control. Vesicourethral reflux had been present in 23% of the children and most had been surgically corrected by either ureteral reimplantation or polytetrafluoroethylene (Teflon) injection. Functioning ventriculoperitoneal shunts were present in 90% of the children with a 1.3 mean revision rate.

Intravesical bladder stimulation was performed according to the methods described by Katona,[8] Madersbacher et al[10] and Kaplan and Richards.[3] The bladder was filled to half the determined capacity with normal saline and an electrocatheter was inserted transurethrally under sterile conditions. The indifferent electrode was placed on the thigh. Bladder stimulation was given in exponential wave forms as previously described by Kaplan and Richards.[3] Stimulation parameters were changed individually in all patients. The range and mean of the stimulation parameters were compared to parameters used by other investigators (table 1). Each session lasted 90 minutes and the patients were treated 5 days per week for 3 weeks. Single channel cystometrics were performed during the bladder stimulation, and the amplitude and number of detrusor contractions, presence of any sensation and post-void residual urine were recorded. Complete urodynamic investigations were performed before the first treatment (1), after the first treatment cycle (2), at the beginning of the second cycle (3) and after the second cycle (4) (fig. 1).

Daily questionnaires were given to the patients and parents to detail any changes noted with stimulation. The following questions were asked: has the patient increased awareness of bladder fullness-sensation; has the frequency of catheterization decreased, increased or remained the same; is the patient wet between catheterization less often or more often, or is it unchanged; does the patient have better, worse or unchanged bowel control, and if the patient has not voided spontaneously at all before treatment does he/she now spontaneously void rarely, commonly or never? In addition, voided and catheterized volumes along with the number of pads or diapers per day was recorded and the data were collected weekly.

TABLE 1. *Comparison of published stimulation parameters*

Parameter	Current Study Range (av.)	Kaplan and Richards[3]	Katona and Berenyi[8]	Madersbacher et al[10]
Voltage (mA.)	1–7 (3.2)	1–10	0.5–4	1–10
Frequency (Hz.)	40–80 (55.5)	60–90	70–90	70–100
Duration (msec.)	4–6 (5.9)	2–6	6–8	6–8
Rise time (sec.)	1–4 (2.4)	1–3.5	Not available	1–10
Interval (sec.)	1–4 (2.9)	2–4	Not available	1–10

Parameters were changed within given range based on the individual response obtained.

The randomization was done by an independent statistician, and the principal investigators analyzing the urodynamic and questionnaire data did not know whether a patient was in the sham cross-over or the active treatment group. For statistical analyses the 2-tailed Student's t test was used if not otherwise indicated. Data were plotted using the Sigma Plot 4.02 software, and regression and correlation coefficients were calculated by the built-in software.

RESULTS

There were no untoward effects of the stimulation other than 1 easily treated urinary tract infection during the rest interval.

Bladder capacity. Initial cystometric evaluation of the children provided a bladder capacity measurement that was used to calculate the volume of saline to be used during stimulation. Figure 2 illustrates the bladder capacity of all children entered in the study compared to a calculated normal childhood bladder capacity [ml. = 32 ml. × age (years) + 73 ml.].[12,13] As expected, the myelodysplastic children had markedly reduced bladder capacities. The mean bladder capacity for the sham and actively treated groups was compared before and after treatment (table 2). There was no statistically significant increase in bladder capacity with transurethral intravesical bladder stimulation. Measured bladder capacities plotted against age before and after the sham period were similar (fig. 3). Figure 4 represents children initially randomized to the sham arm and then actively treated during the second cycle. No statistically significant change in bladder capacity occurred after stimulation. In children who underwent 2 active treatment cycles no significant change in bladder capacity following bladder stimulation (30 total sessions) was noted (fig. 5).

Detrusor contractions. Detrusor activity on initial urodynamic evaluation was characterized as areflexic (negative) or active (positive) with some uninhibited detrusor contractions. Table 3 shows an even distribution of children in each category.

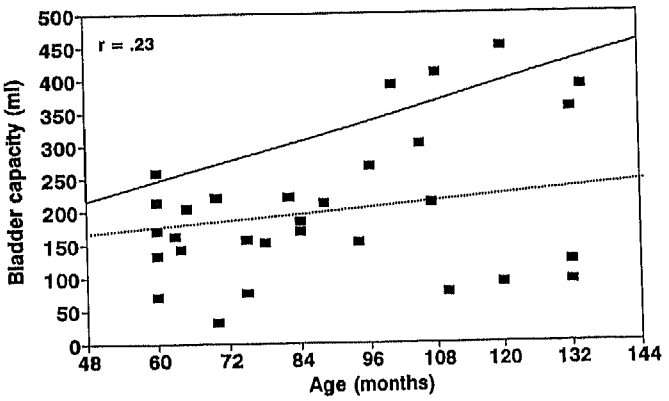

FIG. 2. Correlation between bladder capacity and age (ml. versus month) at initial evaluation in all 31 subjects studied is weak (r = 0.23). Solid line represents normal bladder capacity for children.[12,13]

TABLE 2. *Mean bladder capacity in sham and treated patients*

	Sham		Sham Treated		Treated (series 1)		Treated (series 2)	
	Before	After	Before	After	Before	After	Before	After
Mean (ml.)	218.2	205.8	201.7	191.5	[illegible]	203.1	187.7	[illegible]
Standard deviation (ml.)	87.5	91.7	78.5	61.7	[illegible]	103.8	108.1	[illegible]
Standard error	24.2	25.4	21.8	17.2	[illegible]	24.5	25.5	[illegible]
Maximum (ml.)	388	459	335	313	[illegible]	420	408	[illegible]
Minimum (ml.)	90	96	104	101	[illegible]	40	25	[illegible]
2-tailed Student's t test	p >0.2		p >0.5		p >0.5			

There is no difference in bladder capacity before and after sham treatment, sham active treatment or before and after 2 active treatment cycles of 3 weeks each with a 3-month hiatus (shaded).

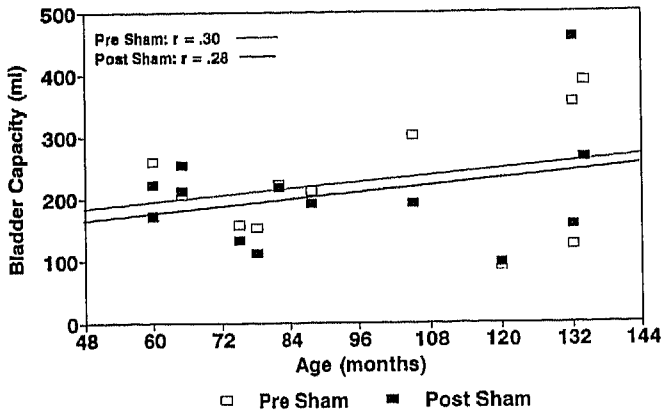

FIG. 3. Correlation of bladder volume and age for 13 sham treated patients before (r = 0.3) and after (r = 0.28) treatment at time points 1 and 2 (see fig. 1) revealed no difference.

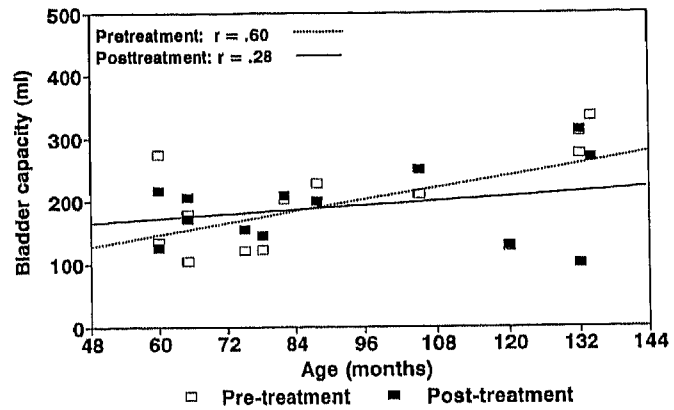

FIG. 4. Correlation of bladder capacity and age for 13 subjects initially sham treated and consequently actively treated after 3-month hiatus at time points 3 and 4 (see fig. 1) revealed no significant differences.

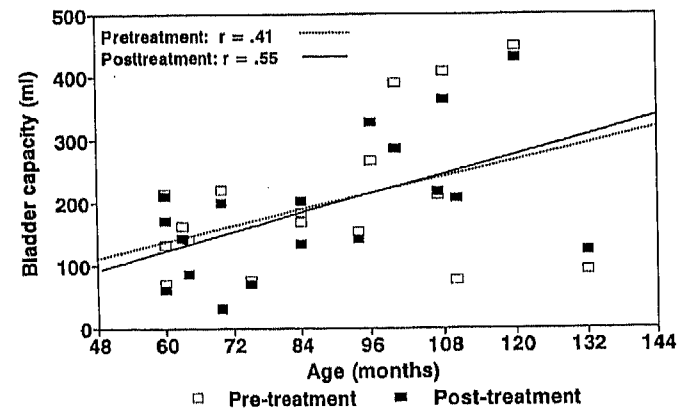

FIG. 5. Correlation of bladder capacity plotted against age in 18 patients who were actively treated during both 3-week sessions interrupted by 3-month hiatus. Data were obtained before initial treatment (time point 1 in fig. 1) and after second treatment cycle (time point 4 in fig. 1).

In the sham group 8 patients had no uninhibited detrusor contractions and 5 had uninhibited detrusor contractions. Of the patients who were treated initially 9 each had and did not have uninhibited detrusor contractions.

Table 4 lists the average number of uninhibited detrusor contractions and the mean pressure of uninhibited detrusor contractions before and after treatment in various subgroups. Of 8 sham treated patients with no uninhibited detrusor contractions (sham negative) before treatment uninhibited detrusor contractions developed after sham stimulation in 4. Of 5 patients with uninhibited detrusor contractions before sham stimulation (sham positive) only 3 continued to have uninhibited detrusor contractions after sham stimulation. After a 3-month rest interval the same 13 patients underwent reevaluation and active treatment. Of 8 patients without uninhibited detrusor contractions on the pretreatment urodynamic study (sham/treatment negative) none had uninhibited detrusor contractions after active bladder stimulation. Of 5 patients with uninhibited detrusor contractions (sham/treatment positive) 4 continued to have uninhibited detrusor contractions after active treatment. The 2 treatment series in the 18 patients undergoing active treatment during both cycles were evaluated separately and labeled as treatment 1 negative/positive and treatment 2 negative/positive. A combined analysis of all 36 treatment cycles revealed no uninhibited detrusor contractions before treatment in 21 of 36 patient observations of which uninhibited detrusor contractions developed after treatment in 8. Of the remaining 15 patient observations with uninhibited detrusor contractions only 9 continued to note these contractions after bladder treatment.

A correlation to subjectively reported presence or absence of bladder awareness (fullness) revealed that of a total available 124 patient observations (before and after treatment) uninhibited detrusor contractions with bladder awareness were noted in 15. No uninhibited detrusor contractions were noted in 32 patient observations but bladder awareness was reported. No uninhibited detrusor contractions and no awareness were revealed in 37 patient observations, and 40 patient observations of uninhibited detrusor contractions indicated no bladder awareness. It is immediately evident that there is no correlation between the presence of uninhibited detrusor contractions and/or the presence or absence of bladder sensory awareness.

TABLE 3. *Bladder activity*

Detrusor Activity	Sham		Treated		Totals
	Before	After	Before	After	
Neg.	8	8	9	11	17
Pos.	5	5	9	7	14
Totals	13		18		31

Negative and positive refer to the presence or absence of bladder activity with urodynamic testing.

TABLE 4. *Number and pressure of uninhibited detrusor contractions before and after treatment in sham active and active active treated patients*

	Pretreatment		Posttreatment	
	No. Uninhibited Detrusor Contractions	Pressure (cm. water)	No. Uninhibited Detrusor Contractions	Pressure (cm. water)
Sham, no detrusor activity	0 (8)	0 (8)	2.8 (4)	24.3 (4)
Sham, detrusor activity	3.8 (5)	19.0 (5)	6.0 (3)	25.0 (3)
Sham/treatment, no detrusor activity	0 (8)	0 (8)	0 (0)	0 (0)
Sham/treatment, detrusor activity	5.6 (5)	22.4 (5)	3.3 (4)	20.0 (4)
Treatment 1, no detrusor activity	0 (10)	0 (10)	6.2 (5)	17.0 (5)
Treatment 1, detrusor activity	6.1 (8)	36.3 (8)	3.7 (6)	42.5 (6)
Treatment 2, no detrusor activity	0 (11)	0 (11)	4.7 (3)	15.0 (3)
Treatment 2, detrusor activity	4.6 (7)	34.3 (7)	7.5 (4)	45.0 (4)

The number in parentheses refers to the number of patients in each category.

Compliance. Terminal bladder compliance was calculated by dividing the bladder capacity by the detrusor pressure when the patient began to leak around the catheter or complain of pain. Figure 6 illustrates compliance in the cross-over group at time points 1, 2, 3 and 4 (fig. 1). The mean compliance was used to compare the patients at each time point and no significant difference was found with treatment among any of the 4 time points (2-tailed Student's t test).

Voiding. Of the 31 children 8 had some measurable spontaneous voiding on entry to the study, including 3 of 13 in the sham arm and 5 of 18 in the treatment arm. In both groups the average measured volume was 75 ml. Neither the treatment nor sham group demonstrated a measurable increase in voided volume. In no case were we able to demonstrate that bladder stimulation restored detrusor function leading to measurable voided volume. Incontinence was assessed by the number of pads used per day and the dryness between catheterizations. We were unable to demonstrate a statistically significant reduction in the number of pads used per day in the bladder stimulated group compared to the sham group.

DISCUSSION

Managing the child with myelodysplasia remains a challenge to the urologist. Abnormalities of bladder sensation, capacity and emptying lead to incontinence, infection, vesicoureteral reflux and stone formation with potential renal failure. Since 1959 Katona and subsequently several other investigators have been using intravesical electrotherapy to treat voiding dysfunction in the myelodysplastic child. This therapy has been used with the theory that bladder stimulation promoted new sensory awareness of bladder filling and a restoration of detrusor contractility. Impressive results with intravesical bladder stimulation have been reported including the achievement of sensation on bladder filling or the urge to void, initiation of bladder contractions and the ability to achieve conscious urinary control.[3-10] Controversial opinions have been published regarding intravesical electrotherapy since it was first used by Katona.[11] In 1975 Katona reported on 100 unselected children with myelomeningocele, most of whom were incontinent of urine, who were subjected to bladder stimulation from 1958 to 1975. He noted that an important development during treatment was the urge to void after several series of bladder stimulation. In conclusion, he reported that 71 of 100 patients had day and nighttime continence after sessions of transurethral intravesical electrotherapy. Nicholas and Eckstein studied 20 children with incontinence secondary to myelomeningocele after 4 weeks of daily bladder electrotherapy.[11] They included continence charts and volumes of urine voided with post-void residual urine. In addition, they performed cystometrics during bladder filling and micturition before and after bladder stimulation. They were unable to demonstrate the disappearance of uninhibited bladder contractions and replacement with normal contractions. Cystometrograms after bladder stimulation failed to show normal contractions in a variety of neuropathic bladder dysfunctions. Since 1984 Kaplan and Richards have pursued intravesical transurethral electrotherapy in the neurogenic bladder with an emphasis on children with myelodysplasia. Madersbacher et al have also accumulated a vast experience with spinal cord injury patients who were rehabilitated with intravesical bladder stimulation.[10] We were encouraged by these reports, and in an effort to evaluate the efficacy of bladder stimulation in children with myelodysplasia we designed this clinical trial. Unfortunately, we have been unable to demonstrate measurable changes with urodynamic evaluation or detailed daily questionnaires. We realize that this study design was rigid in its make-up, and therapy by other investigators has been more individualized for the patient. However, we believed that before undertaking the time and expense of this therapy we should study the possible benefits in a controlled fashion.

Recently Shapiro et al performed a histopathological study on myelomeningocele bladders.[14] The bladders of myelomeningocele patients who underwent augmentation cystoplasty or autopsy were studied with qualitative morphometry, revealing a 3-fold increase in connective tissue in the myelodysplastic bladders compared to normal controls. Data from the autopsy series are somewhat discouraging because they revealed significant connective tissue replacement of the bladder shortly after birth and evidence of bladder damage in the developing fetus. We would have to temper our enthusiasm for bladder stimulation given the results of Shapiro et al and our current clinical findings. However, we intend to pursue more selected therapy for children at an earlier age in hopes that sensory stimulation can be achieved and a lasting effect obtained leading to urinary continence in these children.

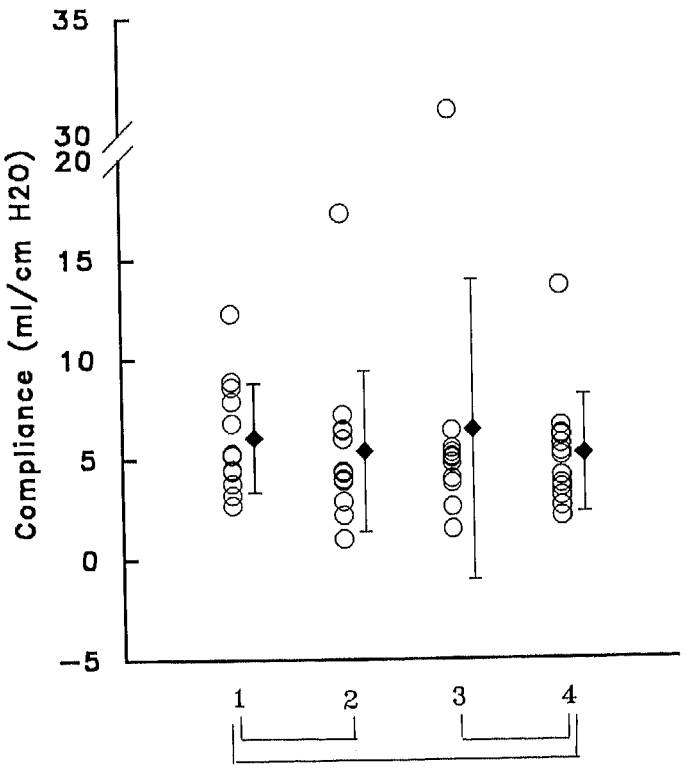

FIG. 6. Bladder compliance [capacity (ml.)/intravesical pressure (cm. water)] for 13 patients in cross-over group at time points 1, 2, 3 and 4. Mean and standard deviation are plotted next to raw data. Student's t test (2-tailed) was used to compare each group. No significant difference was found among any of 4 time points.

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