Research Article

Genital nerve stimulation increases bladder capacity after SCI: A meta-analysis

Dennis J. Bourbeau[1,2,3], Graham H. Creasey[4,5], Steven Sidik[3,6], Steven W. Brose[1,3,7,8], Kenneth J. Gustafson[1,3,9]

[1]Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, USA, [2]Department of Physical Medicine and Rehabilitation, MetroHealth Medical System, Cleveland, Ohio, USA, [3]Cleveland VA Functional Electrical Stimulation Center, Cleveland, Ohio, USA, [4]Department of Neurosurgery, Stanford University, Stanford, California, USA, [5]Spinal Cord Injury Service, VA Palo Alto Health Care System, Palo Alto, California, USA, [6]Department of Mathematics and Statistics, Case Western Reserve University, Cleveland, Ohio, USA, [7]Department of Physical Medicine & Rehabilitation, Case Western Reserve University, Cleveland, Ohio, USA, [8]Ohio University Heritage College of Osteopathic Medicine, Athens, Ohio, USA, [9]Departments of Biomedical Engineering and Urology, Case Western Reserve University, Cleveland, Ohio, USA

Background: Neurogenic detrusor overactivity (NDO) often results in decreased bladder capacity, urinary incontinence, and vesico-ureteral reflux. NDO can trigger autonomic dysreflexia and can impair quality of life. Electrical stimulation of the genital nerves (GNS) acutely inhibits reflex bladder contractions and can increase bladder capacity. Quantifying the effect of GNS on bladder capacity and determining what study factors and subject factors influence bladder capacity improvements will inform the design of clinical GNS interventions.
Methods: We measured bladder capacity in 33 individuals with NDO, with and without GNS. These data were combined with data from seven previous GNS studies (n=64 subjects). A meta-analysis of the increase in bladder capacity and potential experimental factors was conducted (n=97 subjects total).
Results: Bladder capacity increased 131±101 ml with GNS across subjects in all studies. The number of individuals whose bladder capacity was greater than 300 ml increased from 24% to 62% with GNS. Stimulus amplitude was a significant factor predicting bladder capacity gain. The variance of the bladder capacity gain significantly increased with increasing infusion rate. Other factors did not contribute to bladder capacity gain.
Conclusion: GNS acutely increases bladder capacity in individuals with NDO. The consistent increase in magnitude of bladder capacities across the eight studies, and the lack of dependence on individual-specific factors, provide confidence that GNS could be an effective tool for many individuals with NDO. Studies of the chronic effect of GNS on bladder control, with clinical measures such as urinary continence, are needed.

Keywords: Electrical stimulation, Spinal cord injury, Neurogenic bladder, Genital nerve stimulation

Introduction

Neurogenic detrusor overactivity (NDO) can severely impair a person's health and quality of life. Restoring bladder function is considered a high priority by individuals with spinal cord injury (SCI).[1] Individuals typically experience spontaneous and uncontrolled bladder contractions in response to bladder filling, resulting in decreased bladder capacity and urinary incontinence. If bladder contractions are concomitant with reflex contractions of the urethral sphincter, termed detrusor-sphincter dyssynergia, then the individual may have difficulty with bladder emptying. Bladder contractions in these cases are associated with episodes of autonomic dysreflexia and can lead to renal damage.[2] Current interventions, including catheterization strategies, medications, and surgical approaches incompletely address the problem of bladder overactivity and have unwanted side effects.

Electrical stimulation of the genital nerves, which are superficial, is an approach to activate sensory afferents of the genitals in men and women and modulate inhibitory bladder reflex pathways. Genital nerve stimulation (GNS) can inhibit unwanted bladder contractions and

Correspondence to: Dennis J. Bourbeau, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH, USA. Email: dbourbeau@fescenter.org

increase bladder capacity;[3–15] for review see the work by Farag *et al*.[16] Therefore, GNS may provide a therapeutic approach to reduce neurogenic detrusor overactivity and chronic studies should be undertaken. However, concerns remain among clinicians and researchers regarding which individuals are most appropriate for GNS and the dependence of GNS effectiveness on the specific methods used by individual studies. There have been several studies testing GNS acutely, but it is not clear who may benefit from GNS and who should be included in chronic studies of GNS. Understanding the magnitude of the effect of GNS on bladder capacity and the factors involved are required to develop GNS as a clinical intervention. Knowledge of the effect size and variance will improve the design of clinical studies. The purposes of this study were to quantify the amount and variance that GNS increases bladder capacity in individuals with NDO, and determine which subject and study factors affect the improvement in bladder capacity. This study improves the confidence and statistical power of the acute effectiveness of GNS on bladder capacity and provides the evidence required to support the continued conduct of chronic GNS studies.

Methods

For this study, the primary outcome measure was bladder capacity without and with GNS administered during bladder filling. We conducted acute studies to collect new data testing the effectiveness of GNS to increase bladder capacity. We also obtained bladder capacity data from similar published studies testing acute GNS in individuals with NDO. Differences between studies in subject specific factors and study specific factors were identified. We determined that these data sets were comparable and combined them to perform a meta-analysis to quantify the effect of GNS on bladder capacity gain and to determine the effect of factors on the bladder capacity gains.

Effect of GNS on bladder capacity

Experiments were conducted in the urodynamic laboratories of the Cleveland Department of Veterans Affairs Medical Center and the MetroHealth Medical Center in Cleveland, Ohio. Thirty-one male subjects and two female subjects with neurogenic detrusor overactivity were tested (Table 1). Inclusion criteria were (1) complete or incomplete spinal cord injury or multiple sclerosis; (2) neurologically stable; (3) skeletally mature; and (4) reflex bladder contractions confirmed by cystometrogram. Exclusion criteria were (1) active sepsis; (2) active pressure sores; (3) demand pacemaker; (4) low bladder compliance confirmed by cystometrogram; and (5) history of autonomic dysreflexia. Informed consent was obtained from each subject prior to each experiment. Anticholinergics were discontinued at least three days prior to the experiment.

Serial cystometrograms were performed with and without electrical stimulation of the genital nerves. The bladder was emptied by catheterization and room temperature saline was infused into the bladder through a urethral catheter at an infusion rate of 50 ml/min. During cystometric filling the infusion volume, bladder pressure, and rectal pressure were recorded as a function of time on a clinical urodynamic system (Laborie, Mississagua, ON, Canada). Detrusor pressure was calculated as the difference between the bladder and rectal pressures. Cystometric fills were completed before and during electrical stimulation of the dorsal genital nerve. Bladder capacity was defined as the bladder volume at the first distension-evoked reflex bladder contraction. For the purposes of determining bladder capacity, a bladder contraction was defined as an increase in detrusor pressure resulting in leakage or, if no leakage occurred, a detrusor pressure rising above 40 cmH_2O and sustained for at least 10 seconds. Not all subjects had reflex bladder contractions that resulted in leaks; therefore, leak-point volume was not used to determine bladder capacity.

Genital nerve stimulation was delivered via two circular adhesive electrodes, 1 cm in diameter, applied to the dorsum of the penis with the cathode at the base of the penis and the anode 2 cm distal (Natus, Pleasanton, CA). For female participants, one electrode was placed above the clitoris and the second electrode placed laterally on the lower labia majora or the inner thigh. The threshold for the pudendo-anal (PA) reflex was determined: single electrical stimuli were applied to the dorsal genital nerve with increasing amplitude until visible contraction of the anal sphincter was produced. The stimulation amplitude was set to twice the PA threshold amplitude. Five subjects did not demonstrate a PA reflex. These subjects had pelvic sensation and stimulation amplitude was set just below their tolerance limits. Stimulation pulses were monophasic, cathodic, 200 microsecond pulse width square waves. Stimuli were generated by a Digitimer DS7a (Hertfordshire, UK). The mean stimulus amplitude was 26 ± 13 mA. Stimulation was delivered at a frequency of 25 Hz for subjects 1–9, 20 Hz for subjects 10–33. We have conducted a separate study with data from subjects 10–30 and 33 to evaluate perception and tolerance of GNS.

Both conditional and continuous stimulation protocols were performed. For continuous stimulation, GNS was applied continuously for the duration of the

Table 1 Subject characteristics and bladder capacities from new study cohort.

Subject	Sex	Injury	Years Since injury	Initial Bladder Capacity (ml)	Bladder Capacity (ml), Continuous GNS	Bladder Capacity (ml), Conditional GNS
1	M	T9 Complete SCI	1	263	371	*
2	M	T4 Complete SCI	2	210	449	*
3	M	C5-C7 Incomplete SCI	35	352	570	*
4	M	C5-C7 Complete SCI	21	27	135	*
5	M	T-12 Complete SCI	2	378	569	*
6	M	MS	22	434	450	*
7	M	C5 Incomplete SCI	1	113	450	*
8	M	C7 Incomplete SCI	1	433	591	*
9	M	MS	10	30	35	*
10	M	L1 Incomplete SCI	1	249	171	263
11	M	T10 Incomplete SCI	3	181	301	249
12	M	C1 Incomplete SCI	32	187	353	285
13	M	C1 Incomplete SCI	13	479	*	592
14	M	C7 Incomplete SCI	15	401	*	503
15	M	T6-8 Incomplete SCI	13	201	361	298
16	M	C7 Incomplete SCI	1	365	*	546
17	M	T12 Complete	29	584	771	606
18	M	T12 Incomplete SCI	3	295	359	342
19	M	T9 Incomplete SCI	2	409	480	513
20	M	C6 Incomplete SCI	11	272	535	*
21	M	C5 Incomplete SCI	4	125	263	253
22	M	MS	3	47	58	50
23	M	C6 Incomplete SCI	53	138	430	300
24	M	L1 Incomplete SCI	1	496	634	613
25	M	C7 Incomplete SCI	14	125	318	407
26	M	C1 Incomplete SCI	1	203	*	310
27	M	Leukodystrophy	16	485	897	638
28	F	MS	5	239	361	285
29	M	C7 Incomplete SCI	1	249	527	499
30	M	MS	4	179	570	551
31	M	T9 Complete SCI	3	474	*	741
32	F	MS	32	389	*	461
33	M	C5 Incomplete SCI	30	359	455	453

*Stimulus protocol not tested.

cystometric fill trial. For conditional stimulation, GNS was applied at the onset of a contraction, defined as a sudden rise in detrusor pressure of at least 10 cmH_2O. The experimenter made the determination that a sudden rise in detrusor pressure was occurring, and the experimenter manually activated GNS. Trial types included conditional stimulation, continuous stimulation, and no stimulation (control). The first trial was always a control trial, followed by a conditional stimulation trial to find evidence that GNS effectively inhibited that subject's bladder contractions. The remaining tests were randomized. If time was limited, then testing was stopped after at least one fill of each trial type was obtained. In a few subjects that would only use one method (conditional or continuous) of stimulation for take-home chronic GNS, only that method was tested (Table 1). The bladder capacities from all trials using conditional or continuous GNS were averaged together for each subject and taken as the bladder capacity for that subject in response to GNS.

Study selection for pooled data analysis

A literature search was performed using PubMed (1980–2016) for studies testing acute surface GNS to improve bladder capacity in individuals with diagnosed NDO. Seven prospective cohort studies, testing a total of 64 participants, were included[3–6,8,17,18] (Table 2).

There were no substantial differences between studies in general study design or inclusion and exclusion criteria and individuals were neurologically stable. Data were collected during cystometric filling with and without stimulation. Surface stimulation was applied using similar methods in these studies. There was no substantial variation in the electrode size and configuration used. Differences between studies in subject specific factors and study specific factors were identified.

Data analysis

A meta-analysis was performed that included the seven published prospective cohort studies and our new cohort data set testing the effect of acute genital nerve stimulation on bladder capacity. Bladder Capacity Gain,

Table 2 Details of the cohort studies included in the meta-analysis.

Reference	Subject Sex	Subject Injury	Stimulation Frequency, Pulse Width, Amplitude	Infusion Rate (ml/min)	GNS Protocol
Wheeler *et al.* 1992	6 M	3 complete SCI 3 incomplete SCI	5 Hz, 0.35 ms, 25–70 mA	60	Continuous
Previnaire *et al.* 1996	1 F, 9 M	7 complete SCI 3 incomplete SCI	5 Hz, 0.5 ms, 28–80 mA	50	Continuous
Kirkham *et al.* 2001	6 M	complete and incomplete SCI	15 Hz, 0.2 ms, 20–60 mA	10	Continuous and Conditional
Dalmose *et al.* 2003	4 F, 6 M	8 complete SCI 2 incomplete SCI	20 Hz, 0.2 ms, 20–50 mA	60	Conditional
Lee *et al.* 2003	8 M	3 complete SCI, 5 incomplete SCI	25 Hz, 0.25 ms, *	30	Conditional
Fjorback *et al.* 2006	3 F, 4 M	MS	20 Hz, 0.2 ms, 50–60 mA	2–13	Conditional
Opisso *et al.* 2008	4 F, 13 M	complete SCI, incomplete SCI, MS, myelitis, stroke	20 Hz, 0.2 ms, 20–60 mA	30	Conditional

*Stimulus amplitude data not provided for this study.

defined as the difference between the bladder capacity with stimulation and the bladder capacity without stimulation, was used as the common outcome measure. Analyses were conducted using the Metafor package of the R statistical language (R Foundation for Statistical Computing, Vienna, Austria).[19] P-values less than 0.05 were considered significant.

First, we determined that the data sets were consistent and could be pooled together for analysis of contributing factors to Bladder Capacity Gain. We verified that it was reasonable to pool these data together and that assumptions for performing an analysis of variance (ANOVA) were met. We determined that the mean of the Bladder Capacity Gains were sufficiently homogeneous across study cohorts (Cochran's test for heterogeneity, $Q = 12.1$, $P = 0.0973$). We then determined that the data followed normal distributions within each study cohort, with a common variance across study cohorts ($P = 0.31$ Levene's test for homogeneity of variance). The P-value for the Cochran's test is low, suggesting possible heterogeneity between studies. After re-running analyses with one study omitted each time with no significant effect on the Results, no studies were omitted from the meta-analysis. A factor or difference between these studies that would account for potential heterogeneity was not found.

Using ANOVA, study-specific factors and subject-specific factors were tested to determine if they contributed to the variance of the bladder capacity gain. The prospective cohort studies reported individual data on multiple covariate variables. Therefore, we were able to investigate potential relationships between these variables and Bladder Capacity Gain. Subject-specific factors were variables that varied among the total pool of subjects across studies, including sex, age, years since injury, initial bladder capacity (without stimulation), neuropathological origin of NDO (SCI or non-SCI), lesion level, and lesion completeness. The study-specific factors included variables that changed based on the study, including study, infusion rate, stimulation frequency, stimulation pulse width, stimulation amplitude, and stimulation protocol (continuous or conditional). Not all studies reported all factors. Data from these studies were not included in the analysis of a particular factor if those data were not available. Factors that contributed to the variance with a P-value below 0.05 were taken to be predictive of bladder capacity gain. Finally, the bladder capacity that was achieved with GNS was examined to determine if the factors significantly accounted for the variance in the Bladder Capacity Gains. Results are reported as mean ± standard deviation.

Results

Bladder capacities increased with GNS

GNS increased bladder capacity in all studies. In our own cohort of subjects, the bladder capacities increased from a baseline of 284 ± 148 ml to 432 ± 179 ml with GNS, which represented a Bladder Capacity Gain of 148 ± 97 ml (95% confidence interval (118, 178) for those 33 subjects (Fig. 1).

Across studies, the mean bladder capacity increased from 212 ± 131 ml without GNS to 343 ± 159 ml with GNS. The overall mean Bladder Capacity Gain was

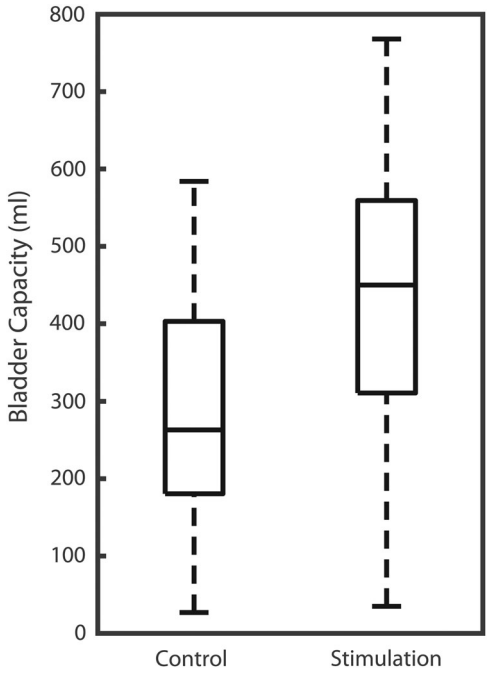

Figure 1 Bladder capacities increased from a baseline of 284 ± 148 ml (control) to 432 ± 179 ml (stimulation) in response to GNS (n = 33) in the current Bourbeau *et al*. cohort (P<0.001). The boxplot shows the 10th, 25th, 50th, 75th, and 90th quartiles for the distributions of bladder capacities without and with stimulation. Genital nerve stimulation (GNS) achieved Bladder Capacity Gains of 148 ± 97 ml. This increase in bladder capacity is the primary outcome measure used for the meta analysis.

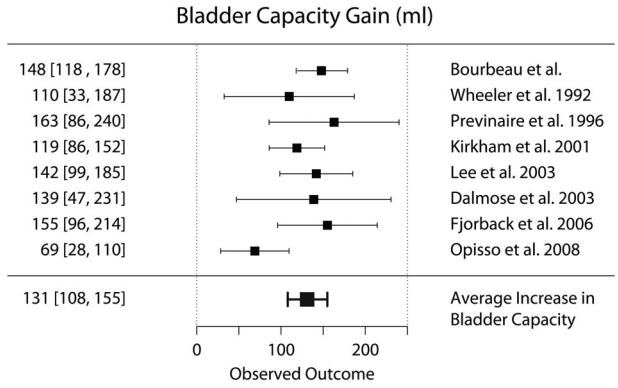

Figure 2 Bladder capacity gains and 95% confidence intervals are shown for the current study and seven other studies (n = 97 subjects total). Mean Bladder Capacity Gain for all subjects (n = 97) was 131±101 ml (108 – 155 95% confidence interval). Bourbeau *et al*. are data from the current study and shown in Figure 1. These data provide confidence in the amount and variance for improvements in bladder capacity from GNS. No studies were statistically different from the pooled mean. The consistency of the bladder capacity gain across multiple studies suggests that GNS may be effective for the majority of individuals with SCI and NDO.

131 ± 101 ml (95% confidence interval (108, 155) (Fig. 2). Bladder Capacity Gains from individual studies ranged from 69 ml to 163 ml and the standard deviations ranged from 58 to 148 ml (Fig. 2).

The distribution of individual subject bladder capacities increased so that most individuals reached clinically acceptable bladder capacities. Bladder capacity increased by at least 50 ml in 79/97 (81%) of individual subjects. Without stimulation, 23/97 (24%) of individuals could achieve 300 ml bladder capacity, 11/97 (11%) of individuals could achieve 400 ml, and 2/97 (2%) could achieve 500 ml. With GNS, 60/97 (62%), 33/97 (34%), and (23/97 (24%) could achieve bladder capacities of 300 ml, 400 ml, and 500 ml, respectively (Figure 3).

Factors predicting Bladder Capacity Gain

Stimulus amplitude was a significant factor (P-value = 0.013), such that increasing stimulation amplitude resulted in increased Bladder Capacity Gains (2.03 ml/mA, 95% confidence interval 0.46, 3.60) (Table 3). All the other subject and study factors, including sex, initial bladder capacity, lesion level, lesion completeness, neuropathological origin of NDO, bladder infusion rate, stimulation protocol (continuous or conditional), stimulation pulse width, and stimulation frequency, were not significant factors.

Although infusion rate did not have a significant effect on the mean of Bladder Capacity Gain, increased infusion rate resulted in increased variability in Bladder Capacity Gain 0.014 ml/(ml/min) (Fig. 4). No other

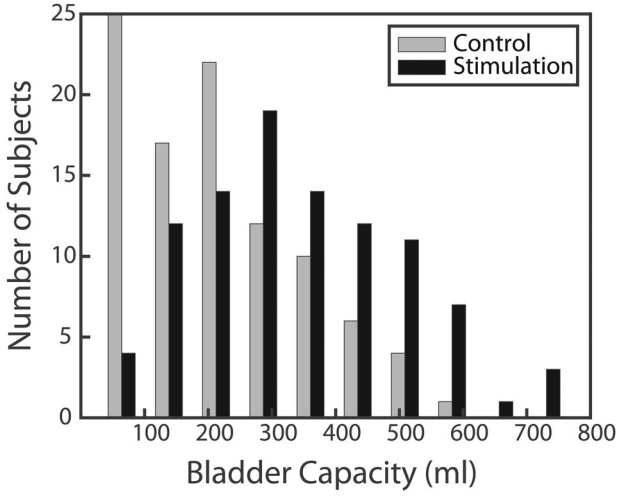

Figure 3 The distribution of bladder capacities achieved with genital nerve stimulation (GNS) increased. Most individuals reached clinically acceptable bladder capacities. Bladder capacity increased by at least 50 ml in 79/97 (81%) of individuals. The number of individuals whose bladder capacity was greater than 300 ml increased from 23/97 (24%) to 60/97 (62%) with GNS. 400 ml: 11/97 (11%) to 33/97 (34%). 500 ml: 2/97 (2%) to 23/97 (24%).

Table 3 Contribution of factors to Bladder Capacity Gains.

Factor	P-value
Subject factors	
Lesion Level	0.075
Age	0.138
Initial Bladder Capacity	0.24
Lesion Completeness	0.27
Sex	0.56
SCI/non-SCI	0.97
Years since injury	0.979
Study factors	
Infusion Rate (std dev)	<0.001
Amplitude Study	0.013 0.097
Pulse width	0.205
Stimulation Protocol	0.36
Infusion Rate	0.46
Frequency	0.81

factors significantly affected Bladder Capacity Gain variability. Thus, changes in infusion rate might not correspond to changes in the mean of Bladder Capacity Gain, but to changes in the standard deviation, or precision, of the measured Bladder Capacity Gain.

Discussion

Genital nerve stimulation (GNS) has been tested by several groups in acute urodynamic studies to inhibit neurogenic detrusor overactivity and increase bladder capacity. These studies included small numbers of subjects, which limited the confidence of the outcome and were not able to test potential factors contributing to bladder capacity gain. Our new data and meta-analysis show that bladder capacity gain with GNS is clinically significant and consistent. Subject-specific factors were not correlated with Bladder Capacity Gain, suggesting that GNS may be effective for a variety of people with NDO. Most study-specific factors did not significantly affect Bladder Capacity Gain. However, infusion rate was positively correlated with the variance in the bladder capacity gain, and stimulation amplitude had a small, significant positive effect, suggesting that increasing stimulus amplitude can increase bladder inhibition. These results add approximately 50% more subjects to the data in the literature to provide a more confident estimate of Bladder Capacity Gain with GNS and to test potential contributing factors.

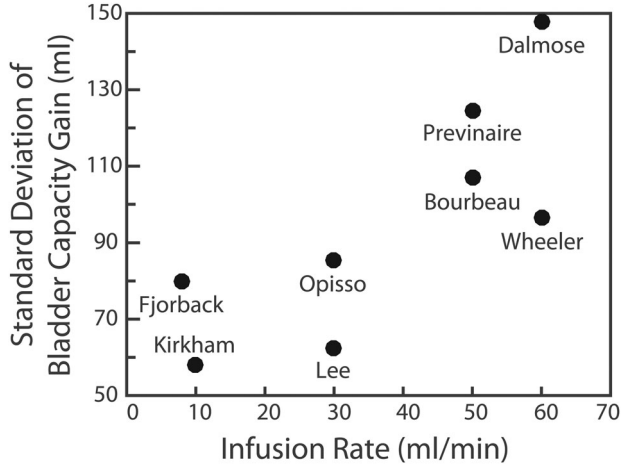

Figure 4 Increasing bladder infusion rates during urodynamic studies increased the variance of the Bladder Capacity Gains by 0.014 ml/(ml/min). Data are grouped by study cohort (n = 8). Infusion rate did not affect the magnitude of the Bladder Capacity Gain. Therefore, larger infusion rates may increase the standard deviation, or precision, of the measured Bladder Capacity Gain and may affect statistical power.

Bladder Capacity Gains

We conducted our own urodynamics experiments, testing the effect of GNS on bladder capacity gain. In our cohort, we found a significant improvement in bladder capacity (Fig. 1), which was consistent with the literature (Fig. 2). Overall, Bladder Capacity Gains were 131 ± 101 ml with GNS (n = 97). For most individuals, this Bladder Capacity Gain represents a significant improvement over their initial or baseline bladder capacities. Figure 3 illustrates the potential clinical effectiveness of GNS. In the absence of stimulation, few individuals achieved bladder capacities of even 300 ml. With GNS, more individuals could achieve more normal bladder capacities of over 300, 400, or even over 500 ml. Therefore, the increase in bladder capacity may be expected to have a clinical benefit in the majority of individuals with NDO.

Although there is no accepted clinical standard or "target" for bladder capacity in subjects with SCI, approximately 300 ml is commonly cited as a clinically acceptable bladder capacity, with some variation due to age and bodyweight. Increasing bladder capacity from 225 to 441 ml in 231 subjects with SCI using a pharmacologic intervention was viewed as successful.[20] Surgical interventions resulting in bladder capacities of 293 ± 118 ml and 312 ± 85 ml,[21] and 392 ml[22] were considered effective. A bladder management system for treatment of urinary retention excluded persons with a bladder capacity greater than 300 ml.[23] Therefore, we reported across a range (300–500 mL) of values.

It is not surprising that we observed an overall strong increase in bladder capacity with GNS because the literature has already reported that inhibiting bladder activity with GNS can result in increased bladder capacities. This analysis shows how robust the effect is by combining results from multiple studies. With a large number of observations, we are able to provide a

more confident representation of the distribution of bladder capacities without and with GNS than any one study in the literature. These data can be used to power future chronic studies.

Serial cystometrograms have the potential to stretch the bladder and result in increased bladder capacities, which would confound our results due to electrical stimulation. To diminish this potential effect of repeated bladder filling and stretching, we randomized our trials after the first Control and first Stimulation trial, and we waited at least 10–20 minutes between trials. This study design for acute testing is consistent with the literature, including the studies whose data are incorporated into this meta-analysis. To verify that inclusion of the first two nonrandomized trials in our bladder capacity data did not significantly affect our results and conclusions, and therefore verify that repeated bladder filling did not constitute a significant confound in our data, we reran the analysis of our data set without those initial trials. An analysis of variance demonstrated a significant increase ($P=0.0148$) from bladder capacities without stimulation (317 ± 195 ml) to bladder capacities with stimulation (422 ± 184 ml). Therefore, data were not significantly confounded by repeated bladder filling.

Subject-specific factors

None of the subject-specific variables were found to be significant factors predicting the mean Bladder Capacity Gain. Subject-specific factors that we tested included sex, initial bladder capacity (without stimulation), SCI lesion level, SCI lesion completeness, and neuropathological origin of NDO (SCI versus non-SCI), which varied within the study populations. There may have been unmeasured factors that contributed to the variance in bladder capacity measurements, but the factors reported here are typically taken into consideration when determining strategies for clinical care. Therefore, GNS is not expected to be limited to certain populations, but potentially effective in anyone with NDO.

We expected that GNS would not be as effective for individuals with lesions of the sacral or lower lumbar cord because the mechanism underlying GNS involves modulating spinal reflex pathways that would be disrupted by a lesion at that level.[24–26] Individuals tested in these studies typically had lesions in the cervical or thoracic spinal cord, which would spare bladder reflexes. Individuals with lower lumbar or sacral spinal cord lesions would not likely be enrolled in a study testing GNS for inhibiting unwanted bladder reflexes because those individuals would not likely have bladder reflexes.

We tested initial bladder capacity without stimulation as a potential factor because we thought that individuals with an already large bladder capacity would achieve smaller Bladder Capacity Gains than individuals with smaller bladder capacities. That is, we assumed that there would be diminishing improvements for individuals who were closer to having normal bladder capacities. On the contrary, initial bladder capacity did not predict bladder capacity gains. GNS has similar potential benefits regardless of individual initial bladder capacity. There may have been some undetected correlation between sex and initial capacity because men tend to have larger bladder capacities than women, but we did not observe this correlation in our analysis.

It was also reasonable to expect that individuals with a very small initial bladder capacity might not achieve any change in bladder capacity in response to GNS. Individuals, such as those who have used a Foley catheter for an extended period, may have fibrotic bladders, resulting in low bladder capacities and low bladder compliances. However, not all low-capacity bladders are fibrotic and it can be challenging to identify these bladders. To our knowledge, the literature does not report a particular minimum bladder capacity under which GNS will not have an effect. Therefore, individuals were included in this analysis regardless of initial bladder capacity. One of the benefits of pooling data from multiple studies is the ability to examine factors such as low bladder capacities. Since only three subjects had such a small bladder capacity and one of them did demonstrate a marked improvement in bladder capacity, we could not draw conclusions regarding a minimum threshold for initial bladder capacity.

Study-specific factors

Our meta-analysis showed that the stimulation amplitude was positively correlated with Bladder Capacity Gain, which is consistent with Previnaire *et al.*[4] It appears that for every 5 mA increase in stimulus amplitude, an individual could experience approximately 10 ml increase in Bladder Capacity Gain. Thus, if an individual can increase the stimulus amplitude from 20 mA to 40 mA, they may experience an additional Bladder Capacity Gain of approximately 40 ml. However, there is not sufficient data to predict Bladder Capacity Gain as a function of stimulus amplitude. Investigators usually choose a minimum amplitude based on the pudendal anal reflex evoked by GNS, and by trial and error. Once an amplitude is chosen and shown to effectively inhibit bladder activity, it is

usually not increased or decreased significantly. Therefore, it is difficult to predict how much Bladder Capacity Gain will increase for an individual if they increase stimulus amplitude, what the minimum stimulus amplitude should be for clinical effectiveness, or if there is a maximum stimulus amplitude beyond which no additional bladder inhibitory effect is achieved. A chronic take-home study could be designed to encourage users to adjust stimulus amplitude as needed and report their strategy for adjusting the amplitude and the clinical outcomes achieved.

Stimulation amplitude and pulse width are not independent. The total charge applied during stimulation, which is determined by the stimulus amplitude and pulse width, results in activation of the neuronal fibers that drive the inhibitory reflex. Therefore, we may expect that pulse width is an important factor. We did not find a relationship between pulse width and Bladder Capacity Gain, but we were not able to rule out such a relationship because pulse width parameters were chosen over a small range, which was appropriate for recruiting the larger neurons that are thought to drive the inhibitory reflex. It is possible that testing pulse widths over a larger range might show a relationship between pulse width and Bladder Capacity Gain.

Infusion rate varied significantly between studies (2–60 ml/min), and this variable correlated positively with the variance, but not the mean, of Bladder Capacity Gain. Faster infusion rates are typically used experimentally to increase the rate of data collection, allowing for more data from cystometric fills while keeping experiment session durations to a minimum for subject comfort. It is possible that faster infusion rates, which are less physiological may provoke bladder contractions more unpredictably, thus increasing the variability of bladder capacity gains while not affecting the mean. Therefore, this parameter should be carefully considered when performing urodynamics procedures.

The stimulus protocol (i.e. conditional or continuous stimulation) was not a significant factor. However, multiple groups are testing conditional stimulation.[6–10,14,18,27,28] Inhibiting the bladder on condition of a feedback signal, such as a bladder contraction, approximates normal bladder control and is efficient. Repeat or constant sensory nerve stimulation also creates the potential for habituation, which could diminish the effectiveness of stimulation approaches such as GNS. Conditional stimulation reduces stimulation time and can avoid the potential for habituation. Studies of chronic GNS will be needed to determine if habituation occurs and limits effectiveness of GNS.

Clinical impact

GNS effectively inhibits unwanted bladder contractions and improves bladder capacity acutely. However, the effectiveness and feasibility of GNS to improve bladder control chronically is not clear. Chronic studies are needed to determine the effect of GNS on bladder capacity. Habituation may occur and diminish the effectiveness of this approach. Other outcome measures should also be considered for inhibiting neurogenic detrusor overactivity, such as improved urinary continence or decreased catheterization frequency, which might be demonstrated over a chronic study. The feasibility of using GNS and its impact on quality of life also need to be studied. GNS could become a part of an individual's bladder management strategy or affect their ability to perform tasks of daily living. Finally, this meta-analysis shows the factors that should be reported and considered when conducting a chronic GNS study.

Conclusion

GNS effectively inhibits detrusor activity via spinal reflex pathways, which results in increased bladder capacity in individuals with NDO. The increase in bladder capacity was consistent across several studies. We are able to report an estimate and distribution of Bladder Capacity Gain with greater confidence, and test potentially contributing factors, by including a large number of subjects compared to smaller studies in the literature. The mean Bladder Capacity Gain depended on stimulus amplitude and the variance depended on bladder infusion rate during cystometrograms. Bladder Capacity Gain did not depend on the other study-specific factors or any subject-specific factors that we tested. Many individuals with NDO may experience the benefits of GNS and a chronic study should be conducted to determine the feasibility, chronic effectiveness, and impact on quality of life of this approach.

Acknowledgements

This work was supported in part by Merit Reviews RX000822, B6685R, B3675R, and B2713R, and Career Development Awards RX000960 and RX001962 from the U.S. Department of Veterans Affairs Rehabilitation Research and Development Service; and by R01 DK077089 from the U.S. National Institutes of Health. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government. The authors would like to thank Melissa Schmitt, RN, Elizabeth Harpster, Katherine Berry, and Michael Jacobson for

assistance with conducting experiments and processing data.

Disclaimer statements

Contributors None.

Funding This work was supported in part by Merit Reviews RX000822, B6685R, B3675R, and B2713R, and Career Development Awards RX000960 and RX001962 from the U.S. Department of Veterans Affairs Rehabilitation Research and Development Service; and by R01 DK077089 from the U.S. National Institutes of Health. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Conflict of interest None.

Ethics approval None.

References

1 Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 2004;21(10):1371–83.
2 Guideline CP, Providers H. *Bladder Management for Adults with Spinal Cord Injury*. Vol 29.; 2006.
3 Wheeler J, Walter J, Zaszczurynski P. Bladder inhibition by penile nerve stimulation in spinal cord injury patients. J Urol 1992;147(1): 100–3.
4 Previnaire J, Soler J, Perrigot M, Boileau G, Delahaye H, Schumacker P, *et al.* Short-term effect of pudendal nerve electrical stimulation on detrusor hyperreflexia in spinal cord injury patients: importance of current strength. Paraplegia 1996;34(2):95–9.
5 Kirkham AP, Shah NC, Knight SL, Shah PJ, Craggs MD. The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury. Spinal Cord 2001;39(8):420–8.
6 Dalmose AL, Rijkhoff NJ, Kirkeby HJ, Nohr M, Sinkjaer T, Djurhuus JC. Conditional stimulation of the dorsal penile/clitoral nerve may increase cystometric capacity in patients with spinal cord injury. Neurourol Urodyn 2003;22(2):130–7.
7 Hansen J, Media S, Nøhr M, Biering-Sørensen F, Sinkjaer T, Rijkhoff NJ. Treatment of neurogenic detrusor overactivity in spinal cord injured patients by conditional electrical stimulation. J Urol 2005;173(6):2035–9.
8 Opisso E, Borau A, Rodríguez A, Hansen J, Rijkhoff NJ. Patient controlled versus automatic stimulation of pudendal nerve afferents to treat neurogenic detrusor overactivity. J Urol 2008;180(4): 1403–8.
9 Horvath EE, Yoo PB, Amundsen CL, Webster GD, Grill WM. Conditional and continuous electrical stimulation increase cystometric capacity in persons with spinal cord injury. Neurourol Urodyn 2010;29(3):401–7.
10 Lee Y, Kim JM, Im HT, Lee K, Kim SH, Hur DM. Semiconditional electrical stimulation of pudendal nerve afferents stimulation to manage neurogenic detrusor overactivity in patients with spinal cord injury. Ann Rehabil Med 2011;35(5):605–12.
11 Wheeler J, Walter J, Sibley P. Management of incontinent SCI patients with penile stimulation: preliminary results. J Am Paraplegia Soc 1994;17(2):55–9.
12 Lee YH, Creasey GH. Self-controlled dorsal penile nerve stimulation to inhibit bladder hyperreflexia in incomplete spinal cord injury: A case report. Arch Phys Med Rehabil 2002;83(2):273–7.
13 Goldman HB, Amundsen CL, Mangel J, Grill J, Bennett M, Gustafson KJ, *et al.* Dorsal genital nerve stimulation for the treatment of overactive bladder symptoms. Neurourol Urodyn 2008;27 (6):499–503.
14 Lee Y-H, Kim S-H, Kim JM, Im HT, Choi IS, Lee KW. The effect of semiconditional dorsal penile nerve electrical stimulation on capacity and compliance of the bladder with deformity in spinal cord injury patients: a pilot study. Spinal Cord 2012;50(4):289–93.
15 Opisso E, Borau A, Rijkhoff NJ. Subject-Controlled stimulation of dorsal genital nerve to treat neurogenic detrusor overactivity at home. Neurourol Urodyn 2013;32(7):1004–9.
16 Farag FF, Martens FMJ, Rijkhoff NJ, Heesakkers JPF. Dorsal genital nerve stimulation in patients with detrusor overactivity: a systematic review. Curr Urol Rep 2012;13(5):385–8.
17 Lee Y-H, Creasey GH, Lim H, Song J, Song K, Kim J. Detrusor and blood pressure responses to dorsal penile nerve stimulation during hyperreflexic contraction of the bladder in patients with cervical cord injury. Arch Phys Med Rehabil 2003;84(1):136–40.
18 Fjorback MV, Rijkhoff N, Petersen T, Nohr M, Sinkjaer T. Event driven electrical stimulation of the dorsal penile / clitoral nerve for management of neurogenic detrusor overactivity in multiple sclerosis. Neurourol Urodyn 2006;25(4):349–55.
19 Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36(3):1–48.
20 Hadiji N, Previnaire JG, Benbouzid R, Robain G, Leblond C, Mieusset R, *et al.* Are oxybutynin and trospium efficacious in the treatment of detrusor overactivity in spinal cord injury patients? Spinal Cord 2014;52(9):701–5.
21 Koie T, Hatakeyama S, Yoneyama T, Ishimura H, Yamato T, Ohyama C. Experience and functional outcome of modified ileal neobladder in 95 patients. Int J Urol 2006;13(9):1175–9.
22 Hansen MN, Rittig S, Siggaard C, Kamperis K, Hvistendahl G, Schaumburg HL, *et al.* Intra-individual variability in nighttime urine production and functional bladder capacity estimated by home recordings in patients with nocturnal enuresis. J Urol 2001; 166(6):2452–5.
23 Homan HD, Dmochowski R, Cochran JS, Karsh L, Sherman ND, Yalla S. Safety and efficacy of a patient-controlled bladder management system for treating urinary retention in men. Neurourol Urodyn 2016;35(5):630–5.
24 Sundin T, Carlsson C, Kock N. Detrusor inhibition induced from mechanical stimulation of the anal region and from electrical stimulation of pudendal nerve afferents. An experimental study in cats. Invest Urol 1974;11(5):374–8.
25 Lindström S, Fall M, Carlsson CA, Erlandson BE. The neurophysiological basis of bladder inhibition in response to intravaginal electrical stimulation. J Urol 1983;129(2):405–10.
26 Craggs M, Mcfarlane J. Physiological society symposium: The physiology and pathophysiology of the lower urinary tract. Exp Physiol 1999;84(1):149–60.
27 Wenzel BJ, Boggs JW, Gustafson KJ, Grill WM. Closed loop electrical control of urinary continence. J Urol 2006;175(4):1559–63.
28 Hansen J, Borau A, Rodríguez A, Vidal J, Sinkjær T, Rijkhoff NJ. Urethral Sphincter EMG as Event Detector for Neurogenic Detrusor Overactivity. IEEE Trans Biomed Eng 2007;54(7): 1212–9.