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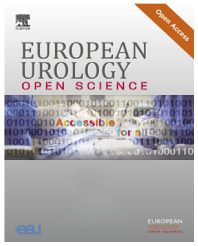

European Association of Urology

Voiding Dysfunction

Self-adjusted Nitrous Oxide During Urodynamic Studies Reduces Patient Pain Without Compromising Study Quality: A Randomized Controlled Trial

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Abstract

Background and objective: A urodynamic study (UDS) is a routine clinic procedure that can cause significant discomfort for certain patients, with no satisfactory analgesic alternatives currently available. Our aim was to evaluate the effectiveness of low-dose self-adjusted nitrous oxide (SANO), titrated to the patient's desired effect, on standard metrics for bladder function and on patient-reported pain and anxiety.
Methods: We conducted a single-institution, double-blind, randomized crossover trial in adults undergoing UDS. Each patient underwent two consecutive UDS runs, randomized to receive oxygen during the first run followed by SANO during the second run, or vice versa. UDS outcomes (capacity, detrusor strength, residual volume) and patient subjective outcomes (Visual Analog Scale for pain and anxiety, operator assessment of verbal feedback) were compared between the two runs. Secondary analyses were performed to compare outcomes during the first UDS run and adjust for treatment order. A paired Wilcoxon signed rank-sum test and McNemar's χ^2 test were used to compare continuous and categorical variables, respectively. Adverse events were recorded.
Key findings and limitations: Nineteen patients were randomized (10 to oxygen for the first run, 9 to SANO for the first run). UDS outcomes did not differ between the two arms. Patients reported significantly less pain during the SANO run than during the oxygen run (p = 0.046). Verbal feedback was significantly better with SANO (p = 0.001). Most patients (15/19, 79%) stated that they would prefer to receive SANO during future UDS. There were no significant complications.
Conclusions and clinical implications: SANO oxide is a safe and effective means of preserving standard adult UDS metrics while significantly reducing patient-reported pain.

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Patient summary: Urodynamic tests (UDS) for evaluation of lower urinary tract symptoms can cause discomfort and pain. Our study shows that nitrous oxide gas self-adjusted by patients had no effect on UDS test outcomes or on verbal feedback during the procedure, and reduced discomfort and pain in comparison to oxygen. Nitrous oxide may an attractive option for patients who are reluctant to undergo UDS.

1. Introduction

A urodynamic study (UDS) is an ambulatory procedure routinely performed to evaluate lower urinary tract symptoms (LUTS). While UDS has low morbidity, up to 40% of patients can find it uncomfortable or painful [1,2] and up to 26% of those undergoing an initial UDS would not choose to undergo the procedure in the future [3]. Pediatric populations may be particularly susceptible to UDS-related discomfort, with studies demonstrating "serious" or "severe" distress in 61% of children undergoing UDS [4]. Embarrassment and discomfort during the procedure are an important concern, as repeated UDS evaluations are often required in patient populations with chronic LUTS, such as individuals with neurogenic bladder [5].

Multiple studies have aimed to reduce patient discomfort during UDS via nonpharmacological means such as heating pads and music therapy, with modest effects [6–8]. Attempts to alleviate discomfort with medications such as propofol are associated with impaired quality of UDS outcomes and elevated residual volume among children undergoing voiding cystourethrography. These complications are not observed with benzodiazepines or midazolam; however, the higher level of sedation with these medications impairs intraprocedural verbal feedback and sensation [2,9].

Outside the USA, nitrous oxide (N_2O) is available as canisters of a 50:50 N_2O/oxygen mixture, with Entonox the prevalent example. Entonox delivery is via a demand regulator connected to the cylinder, which allows patients to control gas release by applying their mask during inhalation. In the USA these mixed-gas canisters lack federal approval and manifold systems are instead used to combine the separate nitrous and oxygen sources. Notably, newer technologies have allowed titration of nitrous levels between 0% and 50%, so patients can leave the mask in place throughout the procedure while customizing the level of gas to achieve the desired effect. In addition to its analgesic properties, N_2O can induce a dissociative euphoria with amnesia and anxiolysis. When administered at concentrations $\leq$50%, N_2O is classified by the American Society of Anesthesiologists (ASA) as "minimal sedation", preserving spontaneous respiration and the patient's ability to provide verbal feedback. Furthermore, N_2O at concentrations $\leq$50% does not require the presence of anesthesia personnel, nil per os status, or transport home [10,11].

Previous studies have demonstrated that self-adjusted nitrous oxide (SANO) reduced pain during transrectal prostate biopsy in comparison to an oxygen control [12]. Little is currently known about the use of N_2O for UDS in adults. The primary aim of this study was to determine whether SANO influences UDS outcome parameters. A secondary goal was determine the effects of SANO on patient pain and anxiety.

We hypothesized that the amnestic and anxiolytic effects of N_2O would improve patient experiences without impacting standard UDS outcomes such as maximum cystometric capacity (MCC), the presence of detrusor overactivity, and the postvoid residual volume (PVR).

2. Patients and methods

2.1. Patient cohort and study design

Internal review board approval was obtained (2022P-000826) and outcomes were reported in accordance with the CONSORT guidelines. Male and female patients aged 21–85 yr who were scheduled for UDS were recruited for study participation from January to March 2023. Patients with medical contraindications to N_2O (Supplementary material) were excluded from the study.

In a study by Broekhuis et al [13], the mean difference in MCC between an initial and a subsequent UDS run was −3 ml (95% confidence interval [CI] −15 to 10), with an interclass correlation coefficient of 0.86. The sample size for detection of an a priori difference of 50 ml was calculated as at least 16 patients per group, with power of 0.82. Randomization was performed according to a 1:1 block model immediately before the start of UDS. Patients were randomized to receive oxygen followed by SANO, or SANO followed by oxygen; the crossover design is illustrated in Figure 1. The procedural team and patient were blinded to the treatment. Muscarinic medications were stopped 24 h before UDS, and patients provided a urine sample to confirm culture negativity. For this study, a Nitrouseal system was used to administer adjustable amounts of N_2O via a single-use disposable mask. The system scavenges exhaled N_2O and limits the maximum amount of N_2O to 50%. After fitting the Nitrouseal mask, the patients were instructed on how to communicate with hand signals throughout the study to titrate the level of gas being administered. Patients received SANO during catheter placement to determine their preferred N_2O level. Following a "washout" period of 2 min, patients underwent two UDS fills according to the randomization scheme. Residual urine was removed between runs using the UDS catheter.

UDS was performed according to the 2012 American Urological Association/Society of Urodynamics, Female

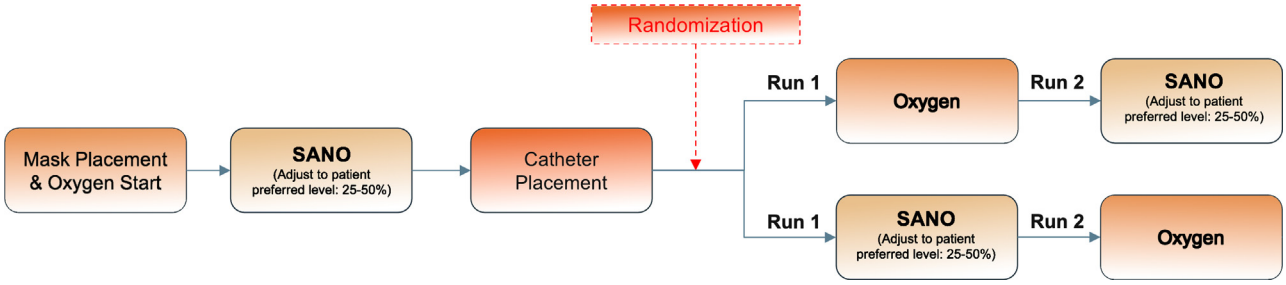

Fig. 1 – Study design. SANO = self-adjusted nitrous oxide.

Pelvic Medicine & Urogenital Reconstruction adult UDS guidelines [14]. All UDS were performed with a Laborie Aquarius XT machine (Laborie Medical, Portsmouth, NH, USA) using 7 Fr dual-lumen fluid-filled urethral catheters, 9 Fr dual-lumen fluid-filled rectal catheters, and electromyography gel-patch electrodes. Filling was performed at 50 cm^3/min with normal saline at room temperature. During the voiding phase, patients were in a sitting or standing position according to their comfort. A nurse practitioner with 32 yr of experience with complex bladder dysfunction performed all studies.

2.2. Outcomes

An intention-to-treat analysis was performed for 19 participants. MCC was measured as the primary outcome. Secondary outcomes included patient-reported pain and anxiety measured at baseline and immediately before maximum capacity during each UDS run using the Visual Analog Scale for Pain (VAS-P; range 0–10) and the Visual Analog Scale for Anxiety (VAS-A; range 0–10).

The blinded UDS operator assessed patient responsiveness (ability to communicate) and tolerance using a 3-point Likert scale as worse than expected, as expected, or better than expected. Standard UDS parameters according to International Continence Society terminology, including first sensation, first desire, strong desire, MCC, bladder compliance (volume/maximum detrusor pressure during filling), detrusor overactivity, detrusor sphincter dyssynergia, inability to void, maximum flow rate, detrusor pressure during the maximum flow rate, voided volume, PVR, and voided percentage were compared for significant differences between the SANO and oxygen runs [15,16]. Postprocedure patient surveys were administered to assess personal experience of catheter placement, desire to have SANO for future UDS, and satisfaction with N_2O levels. Electronic medical records were monitored for Clavien-Dindo graded complications for up to 30 d after UDS.

2.3. Statistical analysis

Bivariate analyses were performed to compare UDS outcomes, pain and anxiety scores, and operator-reported outcomes during SANO and oxygen runs. The paired Wilcoxon signed rank-sum test and McNemar's χ^2 tests were used to compare continuous and categorical variables, respectively. For two variables (patient responsiveness during UDS and patient procedure tolerance observed) there were no categorical responses for the treatment arms. Therefore, zero was substituted with a value of 0.5 to satisfy the χ^2 test conditions. Subgroup analysis was performed to compare key UDS outcomes between treatments for patients randomized to either oxygen or SANO for the first run. In addition, a sensitivity analysis compared UDS outcomes between treatment groups for the first UDS run only. An α value of 0.05 and 95% CIs were used as criteria for statistical significance. For continuous data, a pairwise version of the Hodges-Lehman median difference method was used to estimate a pseudo-median difference and corresponding 95% CI. Data were collected and stored using REDCap electronic data capture tools hosted at Beth Israel Deaconess Medical Center. Analyses were performed using Microsoft Excel v16.66.1, R v4.3.0, and SPSS v29.0.

3. Results

3.1. Baseline patient characteristics

Baseline patient characteristics are summarized in Table 1. Of the 19 patients who provided informed consent, ten were randomized to receive oxygen followed by SANO, and nine were randomized to receive SANO followed by oxygen. All patients elected to adopt a sitting position. No Clavien-Dindo graded complications occurred within 30 d after UDS. All urine cultures obtained immediately before UDS were negative for infection.

3.2. UDS outcomes

There was no significant difference in the primary endpoint of MCC between SANO and oxygen runs. No significant differences were observed for the remaining UDS parameters (Table 2). Two patients were unable to void during the oxygen run but were able to void volitionally during the SANO run. Sensitivity analyses adjusting for randomization did not demonstrate significant differences in UDS parameters according to the treatment order or during the first UDS run (Supplementary material).

3.3. Patient-reported outcomes

The median N_2O concentration chosen by patients during UDS was 37% (interquartile range [IQR] 35–43%; Fig. 2), with a median time to effect of 150 s (IQR 133–196). Patients reported significantly less pain during the SANO run than during the oxygen run (p = 0.047; Table 3 and

Table 1 – Baseline patient characteristics

Parameter	Oxygen First (*n* = 10)	SANO First (*n* = 9)	*p* value [a]
Median age, yr (IQR)	52 (42–60)	65 (62–70)	0.11
Race, *n* (%)			>0.9
Black/African American	1 (10)	0 (0)	
White	9 (90)	9 (100)	
Median baseline VAS-P score (IQR)	1.50 (0.00–2.68)	1.00 (0.00–1.50)	0.9
Median baseline VAS-A score (IQR)	1.35 (0.00–2.93)	2.00 (1.00–3.00)	0.6
Prior Foley catheter, *n* (%)	5 (50)	7 (78%)	0.3
Prior UDS, *n* (%)	2 (20)	3 (33%)	0.6
Median baseline PCS score (IQR)	10.5 (8.3–15.3)	10.0 (6.0–13.0)	0.6
Median baseline STAI score (IQR)	18 (16–18)	15 (13–16)	0.071

IQR = interquartile range; PCS = Pain Catastrophizing Scale; SANO = self-adjusted nitrous oxide; STAI = State-Trait Anxiety Inventory; VAS-A = Visual Analog Scale-Anxiety; VAS-P = Visual Analog Scale-Pain.
[a] Wilcoxon rank-sum test or Fisher's exact test.

Fig. 3). Patients also reported lower anxiety with SANO, but the difference was not statistically significant (p = 0.26; Table 3). The UDS operator rated patient responsiveness and tolerance of the procedure as significantly better than expected during runs with SANO in comparison to runs with oxygen (p = 0.001 and p < 0.001, respectively). While the patients remained blinded to treatment, most correctly identified the order of treatment during UDS runs in the postprocedure interview (15/19, 78.9%).

Immediately after UDS, most patients reported a preference for SANO during any future UDS (15/19, 78.9%). Of the ten patients who previous experience of catheter placement, eight (80%) described their experience as better than previous experiences, while two patients stated that the catheter placement was the same as their previous experience. Most patients wanted no change in the amount of SANO received (10/19, 53%), while 5/19 (26%) would have preferred more, 3/19 (16%) wanted less, and 1/19 (5.3%) were unsure (Table 4).

4. Discussion

4.1. Summary of findings

This is the first prospective, randomized controlled trial demonstrating safe and effective use of patient-adjusted, low-dose (<50%) N_2O during UDS in adults to alleviate pain without compromising UDS quality. Procedure tolerance was significantly better with N_2O, and most patients reported a preference for N_2O again during future UDS.

Minimization of discomfort is critical for patients with complex urological conditions who may require serial UDS. Historically, options for pharmacological sedation during UDS have been limited by adverse impacts on detrusor function or patient inability to provide the verbal feedback needed. N_2O did not affect bladder capacity, bladder contractility, or PVR in our study. Two patients were able to urinate to completion during the N_2O run, but were unable to initiate urination during the oxygen run, which may suggest

Table 2 – Patient urodynamic outcomes by treatment arm

Parameter	Oxygen (*n* = 19)	SANO (*n* = 19)	EMF (95% CI)	*p* value [a]
Filling cystometry				
Median volume, ml (IQR)				
First sensation of bladder filling	205 (81–244)	208 (85–298)	−21 (−64 to 27)	0.48
First desire to void	263 (132–362)	297 (202–362)	16 (−52 to 23)	0.39
Strong desire to void	358 (171–475)	339 (241–414)	7.5 (−38 to 59)	0.89
Median MCC, ml (IQR)	363 (282–553)	402 (307–530)	−17 (−47 to 13)	0.23
Median compliance, ml/cm H_2O (IQR)	37 (25–74)	44 (30–61)	0.10 (−5.3 to 7.3)	0.95
Detrusor overactivity				
Present, *n* (%)	4 (21)	6 (32)	−11% (−44% to 23%)	0.62
Median corresponding volume, ml (IQR)	286 (133–330)	305 (215–335)	−18 (−83 to 55)	0.69
Pressure flow				
Detrusor sphincter dyssynergia, *n* (%)	1 (5)	1 (5)	0% (−31% to 32%)	>0.99
Inability to void, *n* (%)	2 (11)	0 (0)	11% (−23% to 44%)	0.72
Median Q_{max}, ml/s (IQR)	11 (4.9–13)	11 (5.1–19)	−0.30 (−4.5 to 1.4)	0.77
Detrusor pressure at Q_{max}, cm H_2O (IQR)	45 (31–56)	45 (31–61)	−1.0 (−6.0 to 4.0)	0.73
Voiding				
Median voided volume, ml (IQR)	271 (119–448)	306 (155–466)	−18 (−74 to 22)	0.40
Median postvoid residual, ml (IQR)	132 (0.0–221)	57 (0.0–207)	−20.7 (−49.5 to 78.5)	0.66
Median voided percentage (IQR)	75 (50–100)	86 (45–100)	−0.26 (−19 to 14)	>0.99
Median BOOI score (IQR)	24 (8.5–46)	32 (4.1–47)	−2.6 (−7.8 to 6.8)	0.46
Median BCI score (IQR)	101 (72–126)	108 (81–146)	−7.6 (−16 to 6.5)	0.92

BCI = Bladder Contractility Index; BOOI = Bladder Outlet Obstruction Index; CI = confidence interval calculated using the independent-sample Hodges-Lehman method; EMF = estimated median difference; IQR = interquartile range; MCC = maximum cystometric capacity; Qmax = maximum urinary flow rate; SANO = self-adjusted nitrous oxide.
[a] The p values were calculated using a paired Wilcoxon signed rank test for continuous variables or McNemar's χ^2 test with continuity correction for categorical variables.

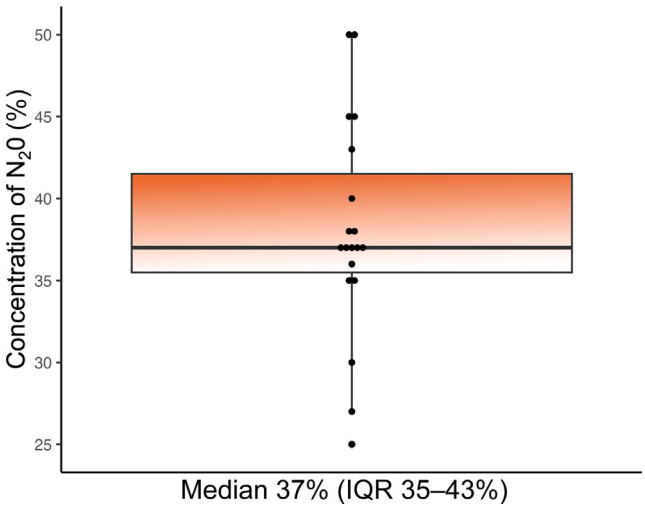

Fig. 2 – Maximum nitrous oxide concentration requested by the 19 patients. IQR = interquartile range.

that the favorable anxiolytic properties of N_2O aid in the ability to complete UDS. In contrast to our findings with N_2O, a study of voiding cystourethrography in children found that propofol prevented voiding to completion in 45% of patients, in comparison to only 11% without propofol [17]. Similar to N_2O in our study, midazolam did not impact standard bladder functional outcomes in children undergoing cystometry [18–20] or voiding cystometrography [19]. However, midazolam is considered moderate sedation by the ASA, and thus requires anesthesia staff, recovery time, and an escort home.

In the present study, N_2O reduced patient perception of pain during UDS. Previous studies investigating adjuvant medication to reduce UDS-associated pain revealed similar results. Saberi et al [21] demonstrated that use of rectal midazolam for women undergoing UDS was associated with a significant decrease in pain, although there was no change in patient stress or collaboration with the operator, in comparison to placebo. Herd et al [2] reported that oral midazolam was significantly associated with lower stress in children undergoing cystourethrography imaging without compromising detection or grading of vesicoureteral reflux. A retrospective review of cystometry studies found no difference in Groningen Distress Rating Scale between children receiving either intramuscular, oral, or rectal midazolam and those receiving no sedation at all [20]. On the basis of these cases, we believe that transient medications with favorable tolerance profiles, such as N_2O, are favorable for improving patient experiences during UDS.

One of the strengths of our study is that N_2O was adjusted to the patient's desired level, which may be expected to decrease the side-effect profile. A 2020 review of N_2O for ambulatory urological procedures revealed that side effects such as nausea, vomiting, headache, and dizziness occurred at rates between <1% and 40% [22]. However, this review included studies with N_2O at concentrations up to 70%, which may have contributed to the large variability in the safety profile. Interestingly, a recent study showed a fourfold increase in side effects with N_2O at 50% in comparison to 25% [23].

There are several practical considerations regarding integration of N_2O into existing clinical workflows. The gas itself is relatively inexpensive, and the presence of anesthesia personnel is not necessary for N_2O at concentrations <50%. In our study, N_2O had an average onset of effect of 2.7 min, in contrast to moderate sedation options such as midazolam and ketamine, which have longer onset and offset times. Many studies examining the offset time for N_2O in terms of return to mental aptitude and ability to drive have shown that full return of function occurs within 4 min. Together, these characteristics make N_2O a relatively cost-effective analgesic.

4.2. Limitations

Our results should be considered in the context of the study limitations. Patients were recruited from a single tertiary institution. The study was powered to assess urodynamic

Table 3 – Patient pain, anxiety, and UDS experience by treatment

Parameter	Oxygen (n = 19)	SANO (n = 19)	EMD (95% CI)	p value [a]
Pain and Anxiety Scores				
Median intraprocedural VAS-P score (IQR)	2.0 (0.0–3.0)	0.7 (0.0–1.3)	1.6 (0.0–2.5)	0.046
Median intraprocedural VAS-A score (IQR)	2.0 (0.0–2.9)	1.0 (0.0–2.2)	0.90 (−0.75 to 2.3)	0.26
Patient responsiveness during UDS, n (%) [b]				<0.001
Better than expected	0 (0)	13 (68)	NA	
As expected	19 (100)	5 (26)	NA	
Worse than expected	0 (0)	1 (5.3)	NA	
Patient procedure tolerance observed, n (%)				<0.001
Better than expected	1 (5.3)	16 (84)	NA	
As expected	18 (95)	3 (16)	NA	
Worse than expected	0 (0)	0 (0)	NA	
Catheter placement tolerance, n (%) [b]				NA
Better than expected	NA	15 (79)	NA	
As expected	NA	3 (16)	NA	
Worse than expected	NA	1 (5)	NA	

CI = confidence interval calculated using the independent-sample Hodges-Lehman method; EMD = estimated median difference; IQR = interquartile range; NA = not applicable; SANO = self-adjusted nitrous oxide; UDS = urodynamics; VAS-A = Visual Analog Scale-Anxiety; VAS-P = Visual Analog Scale-Pain.

[a] The p values were calculated using a paired Wilcoxon signed rank-sum test for continuous variables or McNemar's χ^2 test with continuity correction for categorical variables.

[b] Catheter placement for UDS was observed before UDS, with SANO for all patients.

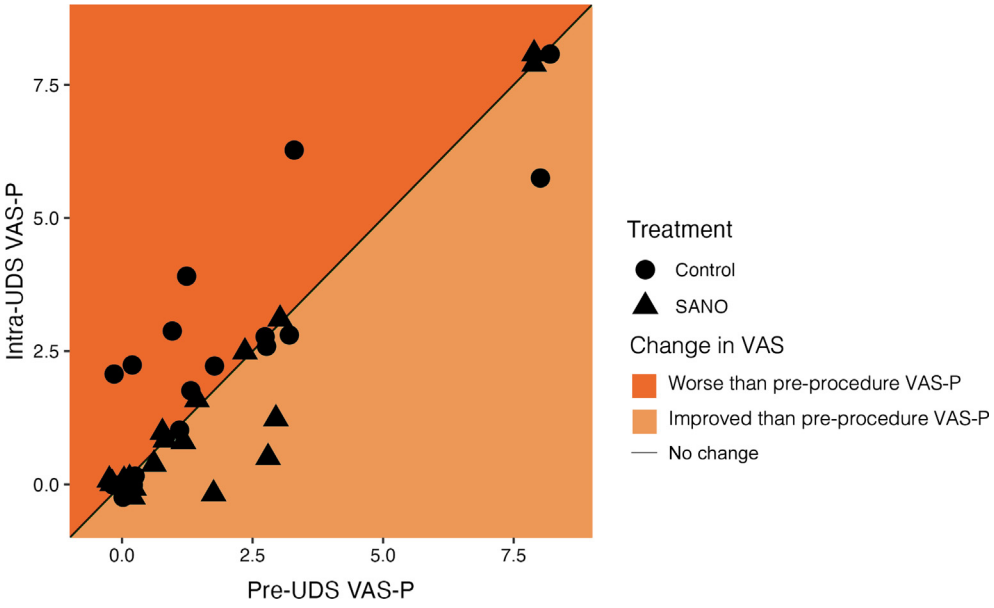

Fig. 3 – Baseline and intra-UDS VAS-P scores by treatment arm. SANO = self-adjusted nitrous oxide; UDS = urodynamics; VAS-P = Visual Analog Scale-Pain.

Table 4 – Questionnaire responses from the 19 patients

Question	Responses,*n* (%)
Patients who correctly identified treatment during UDS runs	15 (78.9)
If you have ever had a catheter placed before the UDS today, how was placement today with SANO compared to the past?	
Better	8/10 (80)
As expected	2/10 (20)
Worse	0/10 (0)
If you had UDS again, would you prefer with or without SANO?	
With SANO	14 (74)
Unsure	3 (16)
Without SANO	2 (11)
Would you have rather received more or less SANO during the UDS?	
No change	10 (53)
More	5 (26)
Less	3 (16)
Not certain	1 (5.3)

SANO = self-administered nitrous oxide; UDS = urodynamics.

capacity outcomes, and the resulting small sample size may have limited the interpretation of other outcomes of interest. In comparison to a study on UDS in women, patients in this cohort had slightly higher baseline anxiety scores (VAS-A 2.0 vs 1.6), which may have influenced the efficacy of N_2O and the patients' overall experience of UDS [5]. Only one patient was found to have detrusor sphincter dyssynergia on UDS testing; therefore, further studies in this patient population are warranted. Similarly, we did not have patients with simple stress urinary incontinence and thus we could not determine whether abdominal leak-point pressure would be recapitulated in this population. Recruitment was limited to adult patients, so the findings may need to be confirmed in a pediatric population. The crossover study design poses the possibility of carryover effects from one treatment arm affecting the second UDS run. This was mitigated via a sufficient washout period between gases, and there was no difference in the sensitivity analysis after adjusting for treatment order or when comparing outcomes during the first run alone. Finally, N_2O has come under scrutiny as a health care greenhouse gas with a carbon footprint [24]; however, the SANO instrumentation used in this study relies on small-volume E canisters, with one canister sufficient for 20–30 procedures, circumventing the large-volume (>95%) N_2O leakage associated with central piped N_2O systems that are common in hospitals [25].

5. Conclusions

For adults undergoing UDS, SANO is a safe and effective means of alleviating pain and improving procedure tolerance without impacting standard UDS metrics. Integration of nitrous oxide into existing clinical workflows may reduce the diagnostic burden for multimorbid patients or those requiring serial UDS. Additional research is needed to validate our findings and translate this treatment to other ambulatory urological procedures and demographic groups.

Author contributions: Heidi J. Rayala had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Escobar, Vasdev, Wang, Rayala.
Acquisition of data: Escobar, Rayala, Gallo.
Analysis and interpretation of data: Escobar, Vasdev, Wang, Rayala.
Drafting of the manuscript: Escobar, Vasdev, Rayala.
Critical revision of the manuscript for important intellectual content: Escobar, Vasdev, Gallo, Softness, Wang, Rayala.
Statistical analysis: Escobar, Vasdev, Wang, Rayala.
Obtaining funding: Rayala.
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Supervision: Rayala, Wang.

Other: None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.08.002.

References

[1] March-Villalba JA, López Salazar A, Romeu Magraner G, et al. Analysis of pain perception associated with urodynamic testing in children over 3 years old. Actas Urol Esp 2021;45:232–8.
[2] Herd DW, McAnulty KA, Keene NA, Sommerville DE. Conscious sedation reduces distress in children undergoing voiding cystourethrography and does not interfere with the diagnosis of vesicoureteric reflux: a randomized controlled study. Am J Roentgenol 2006;187:1621–6.
[3] Yokoyama T, Nozaki K, Nose H, Inoue M, Nishiyama Y, Kumon H. Tolerability and morbidity of urodynamic testing: a questionnaire-based study. Urology 2005;66:74–6.
[4] Herd DW. Anxiety in children undergoing VCUG: sedation or no sedation? Adv Urol 2008;2008:498614.
[5] Yeung JY, Eschenbacher MA, Pauls RN. Pain and embarrassment associated with urodynamic testing in women. Int Urogynecol J 2014;25:645–50.
[6] Kim JW, Kim HJ, Park YJ, et al. The effects of a heating pad on anxiety, pain, and distress during urodynamic study in the female patients with stress urinary incontinence. Neurourol Urodyn 2018;37:997–1001.
[7] Diri MA, Çetinkaya F, Gül M. The effects of listening to music on anxiety, pain, and satisfaction during urodynamic study: a randomized controlled trial. Urol Int 2019;103:444–9.
[8] Öztürk E, Hamidi N, Yikilmaz TN, Özcan C, Başar H. Effect of listening to music on patient anxiety and pain perception during urodynamic study: randomized controlled trial. Low Urin Tract Symptoms 2019;11:39–42.
[9] Stokland E, Andréasson S, Jacobsson B, Jodal U, Ljung B. Sedation with midazolam for voiding cystourethrography in children: a randomised double-blind study. Pediatr Radiol 2003;33:247–9.
[10] Broughton K, Clark AG, Ray AP. Nitrous oxide for labor analgesia: what we know to date. Ochsner J 2020;20:419–21.
[11] Gross JB, Bailey PL, Connis RT, et al. Practice guidelines for sedation and analgesia by non-anesthesiologists: an updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia. Anesthesiology 2002;96:1004–17.
[12] Escobar AJ, Krishna S, Flowers KM, et al. Practical use of self-adjusted nitrous oxide during transrectal prostate biopsy: a double-blind randomized controlled trial. J Urol 2024;211:214–22.
[13] Broekhuis SR, Kluivers KB, Hendriks JC, Massolt ET, Groen J, Vierhout ME. Reproducibility of same session repeated cystometry and pressure-flow studies in women with symptoms of urinary incontinence. Neurourol Urodyn 2010;29:428–31.
[14] Winters JC, Dmochowski RR, Goldman HB, et al. Urodynamic studies in adults: AUA/SUFU guideline. J Urol 2012;188(6 Suppl):2464–72.
[15] D'Ancona C, Haylen B, Oelke M, et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn 2019;38:433–77.
[16] Haylen BT, Maher CF, Barber MD, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). Int Urogynecol J 2016;27:655–94.
[17] Merguerian PA, Corbett ST, Cravero J. Voiding ability using propofol sedation in children undergoing voiding cystourethrograms: a retrospective analysis. J Urol 2006;176:299–302.
[18] Bozkurt P, Kilic N, Kaya G, Yeker Y, Elicevik M, Söylet Y. The effects of intranasal midazolam on urodynamic studies in children. Br J Urol 1996;78:282–6.
[19] Thevaraja AK, Batra YK, Rakesh SV, et al. Comparison of low-dose ketamine to midazolam for sedation during pediatric urodynamic study. Paediatr Anaesth 2013;23:415–21.
[20] Özmert S, Sever F, Tiryaki HT. Evaluation of the effects of sedation administered via three different routes on the procedure, child and parent satisfaction during cystometry. Springerplus 2016;5:1496.
[21] Saberi N, Hayrabedian A, Mazdak H, et al. Effect of rectal midazolam on pain, stress, and cooperation of patient during urodynamic test in women: a randomized clinical trial. Urol J 2023;20:129–34.
[22] Gopalakrishna A, Bole R, Lipworth R, et al. Use of nitrous oxide in office-based urologic procedures: a review. Urology 2020;143:33–41.
[23] Nagele P, Palanca BJ, Gott B, et al. A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression. Sci Transl Med 2021;13:eabe1376.
[24] Ratcliff A, Burns C, Gwinnutt CL. The contribution of medical nitrous oxide to the greenhouse effect. Health Trends 1991;23:119–20.
[25] Seglenieks R, Wong A, Pearson F, et al. Discrepancy between procurement and clinical use of nitrous oxide: waste not, want not. Br J Anaesth 2022;128:e32–4.