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A new bladder-emptying method in females with neurogenic bladder: A randomized, phase II trial

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Abstract

Aim: To evaluate the performance of the new device compared with clean intermittent catheterization (CIC).

Methods: From March 2015 to March 2018, patients who were admitted to the urologic outpatient clinic. A new intraurethral self-retaining device (ISRD) was made of medical grade silicone and it was inspired by similar catheters that use sliding disks to adjust or fix tubes used to drain the bladder. Patients were randomized into two groups (experimental group [GI]-ISRD vs control group [GII]-CIC). The evaluation was performed at the time of enrollment and 6 months after treatment. Intervention was initiated from the antisepsis of the perineal region and subsequent introduction of the device through the external urethral meatus. The primary outcome was quality of life (QOL). Urinary tract infections (UTIs) episodes, data on urodynamic parameters, adverse effects and number of diapers per day.

Results: A total of 177 subjects were analyzed. We found a significant improvement on QOL analysis in the ISRD group ($P < .01$). ISRD group presented an important reduction (two episodes after ISRD use) on number of UTIs ($P < .01$) and diaper use, and significant improvement on bladder capacity (80 mL of the average improvement) ($P < .01$) and compliance ($P = .01$). Among all registered serious adverse effects, ISRD presented with lower proportion.

Conclusions: The new device has shown to be a safe and promising alternative for adequate emptying of the neurogenic bladder in female patients. Our study has a limitation that is related to a limited period of observation.

KEYWORDS

clean intermittent catheterization, neurogenic bladder, new device, quality of life

1 | INTRODUCTION

Neurogenic bladder is characterized by lower urinary tract dysfunction due to neurological impairment.[1] One of the available treatment options is clean intermittent catheterization (CIC), which aims to maintain bladder function as similar as possible to the physiological state in relation to filling and emptying phases.[2,3]

CIC is done at regular intervals that vary according to age, bladder capacity, residual urine volume, and time free from involuntary urine leakage as well as finding a suitable place to perform it. The purpose is to restrain postvoid residual volume by mimicking

normal voiding. These measures result in the reduction of risk of urinary tract infection (UTI).[4,5] However, to be effective, CIC requires regularity, therefore impacting on daily life activities and generating fixed costs to patients and caregivers.[6,7]

Adherence rate is influenced by negative aspects such as the need for preserved cognition, the presence of pain, the possibility of urethral injury. For this reason, CIC could impact daily life activities in some patients.[8,9] To solve these problems, the present study aimed to evaluate the performance of a new intraurethral self-retaining device (ISRD) in the female with neurogenic bladder, as a possible alternative to CIC.

2 | MATERIALS AND METHODS

2.1 | Design and sample selection

A prospective, single-institution, randomized clinical study was performed, including female subjects with neurogenic bladder diagnosis and current use of CIC. From March 2015 to March 2018, all patients admitted to our urologic outpatient clinic who met inclusion criteria were enrolled. Exclusion criteria included symptomatic UTI and history of urothelial tumors.

Subjects were randomized to two groups, either to use the ISRD (experimental group [GI]) or to continue using CIC (control group [GII]). The participants were separated into the groups using a list of random numbers that had been generated using Random Allocation Software, version 1.0. The list was drawn up by a member of the team who was not involved in collecting the data. One researcher determined the group to which the participants would be allocated by consulting the randomization list. The analysis was conducted by protocol and baseline and posttreatment assessments were compared between (ISRD vs CIC) and within groups (pre-post analysis) according to the trial profile (Figure 1).

The institutional review board approved the study protocol and all patients provided written informed consent. The sample size followed determinations of National Agency of Sanitary Surveillance (ANVISA) directed to the type of clinical research phase II: "First controlled studies in patients to demonstrate the potential effectiveness of the medical device (100 to 200 volunteers)." In addition to ANVISA determination, the sample size formula was used to describe the population represented by a quantitative variable, comparing two groups. To satisfy all dimensions, the minimum sample estimated was 94 patients

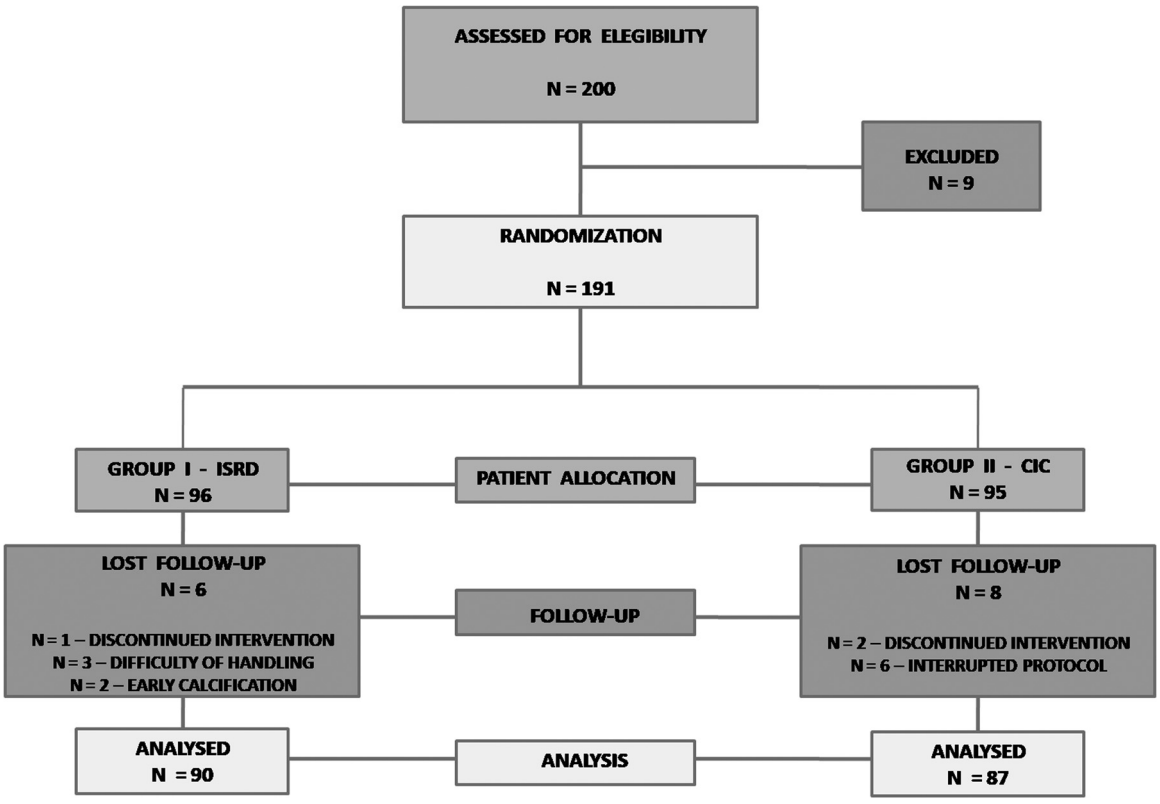

FIGURE 1 Trial profile–Consolidated Standards of Reporting Trials (CONSORT). CIC, clean intermittent catheterization; ISRD, intraurethral self-retaining device

(47 individuals per group). In both groups, all patients had been using oral anticholinergics and this regimen was maintained all the period. None has submitted to botulinum toxin application or another way to control detrusor overactivity.

2.2 | Materials

The ISRD was made of medical grade silicone and is available from 10 to 14 Fr in diameter with four different sizes 3, 3.5, 4, and 4.5 cm, of the distance between disks. Details on manufactured, structure and insertion have been published in previous pilot study.[10] The device structure was formed by two disks (fixed and the other mobile), six collectors of urine, and a cover connected to the lumen of the catheter (Figure 2A). The fixed disk was positioned at the bladder neck from the inside. The mobile one was positioned at the level of the external urethral meatus (Figure 2B).

The urinary catheter used in CIC was typically made of plastic (PVC). The sizes variations were among 8 and 12 Fr, in accordance with the age and urethra size.

2.3 | Insertion technique

The size of ISRD was chosen according to the anatomy of each patient, urethra size, and age. Once the children used the devices of 3 and 3.5 cm and the teenagers and adults used the devices of 4 and 4.5 cm.

ISRD was inserted by simple technique and with local anesthesia, in an outpatient setting and without the need for optical instruments or sedation. The technique of routine asepsis of the genital and perineal region, then urethral lubrication with lidocaine 1% in the form of gel and direct introduction of ISRD coupled in the rigid pusher. After that, the pusher was removed sequentially and the distal disc was adjusted to the size of the urethra.[11]

2.4 | Follow-up

Patient follow-up was performed through presential visits in the third and sixth months previously scheduled, in addition to extra evaluation in cases of intercurrences. The follow-up time was 6 months. This is the recommended period for each ISRD exchange.[11]

2.5 | Measures

All patients had already undergone a complete urological evaluation that included ultrasonography, urodynamics, and cystography. Assessments included quality of life (QOL) analysis, UTIs episodes, urodynamic parameters (bladder capacity and compliance), adverse effects, and quantification of daily diapers used. All patients were followed up for a period of 6 months.

QOL was evaluated with the SF-Qualiveen Questionnaire and was performed at two stages: before and

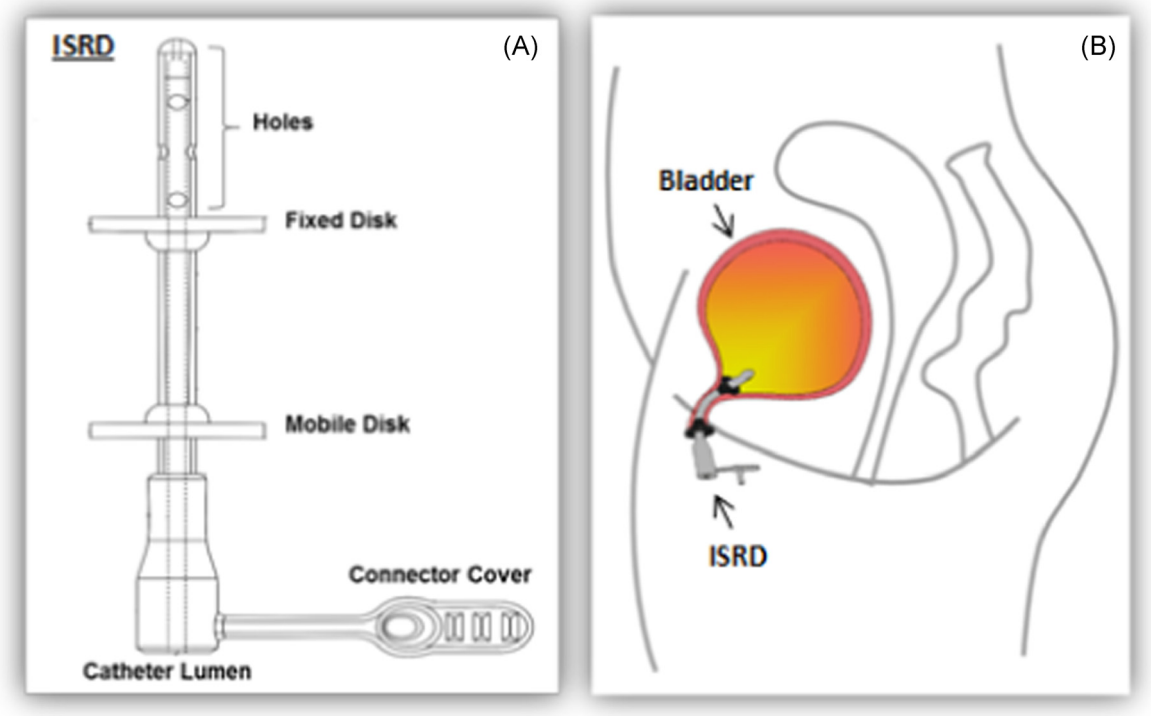

FIGURE 2 Technical drawing of the ISRD (A) and panoramic view of ISRD in situ. ISRD, intraurethral self-retaining device

6 months after implantation of the ISRD. SF-Qualiveen Questionnaire consists of eight items in four domains (1, Limitations; 2, Fear; 3, Feelings; and 4, Impact on daily life). Each domain has been independently validated. The questionnaire was answered by adult patients and by caregivers of younger participants. Caregivers (with a close relationship with the child) were chosen to answer the questionnaire on behalf of younger patients due to the ease of communication and higher response accuracy.

The urodynamic protocol was performed with continuous infusion rate 25 mL/s per infusion pump; urethral catheters of size 4 Fr and rectal 10 Fr. Vesical, abdominal, and flow pressure were measured.

Side effects and adverse events encountered at home or noted by the physician were also reported. Adverse events were defined by Common Terminology Criteria for Adverse Events considering the System Organ Class and individual descriptions.[12] Events were categorized according to their level of severity, as follows: Mild: hematuria, skin excoriations, and/or avulsions of the device; Serious: Fistulas, calcifications, fragmentation of the device, and urinary retention due to obstruction. In case of adverse events associated with the ISRD (technical difficulties, discomfort, pain, urinary leakage, anatomical anomalies, and signs of infection) the treatment was re-evaluated. No patient had previously used other types of indwelling catheter.

2.6 | Outcomes

The primary endpoint was QOL analysis. Secondary outcomes included clinical parameters (UTI episodes, bladder capacity, compliance, and daily diapers used). UTI was defined as the presence of uroculture with 10^5 cfu/mL add the presence of one or more related symptoms (fever, suraubic pain, and burning). Uroculture was performed at the initial, third and sixth month consultations and more whenever symptoms were reported by the patients. Adverse events were monitored to review study performance (data validity and integrity).

2.7 | Statistical analysis

Numerical variables were expressed as mean and standard deviation when they presented normal distribution and were compared either by the unpaired Student *t* test (independent groups) or paired Student *t* test (pre-post analysis). Non-normal variables were expressed as median and interquartile range and were compared by the Mann Whitney *U* test (independent groups) or the Wilcoxon signed-rank test (pre-post analysis). Both intragroup and intergroup analysis was performed. Proportions were evaluated by the χ^2 test or, alternatively, by the Fisher's exact test. All of the above tests were considered statistically significant when $P =< .05$. The software used for analysis was SPSS Version 21.

3 | RESULTS

A total of 177 subjects were included, 91 children (11 ± 6 years) and 86 adults (41 ± 17 years). The most prevalent conditions at baseline evaluation and demographic characteristics are shown on the following Table 1.

3.1 | Quality of life analysis

QOL data was homogeneous between groups at baseline evaluation. In the intergroup analysis at 6 months, the following mean values and standard deviation of the scores were observed for each domain: limitation GI = 2 $\pm$ 0.7 and GII = 7 $\pm$ 0.67; fear G1 = 2.5 $\pm$ 1 and GII = 8 $\pm$ 0.61; feeling G1 = 2 $\pm$ 0.71 and GII = 6 $\pm$ 0.98; impact on daily life G1 = 2.5 $\pm$ 0.89 and G2 = 8 $\pm$ 0.4 (Table 2).

3.2 | Urinary tract infection episodes

The number of UTI episodes was compared between groups (GI and GII) at 6 months, with a significant statistical difference between groups. We found that the ISRD group presented a significant reduction (rate of reduction of two episodes) in the number of episodes after the use of the device (intragroup analysis; Figure 3). Infection reduction was also found in CIC, but less significant than in the other group. The most frequently described pathogen was *Escherichia coli* in both groups.

3.3 | Urodynamic parameters

Bladder capacity and compliance were assessed. In the intragroup analysis (ISRD group) there was a statistically significant increase in bladder capacity when comparing the mean values of baseline evaluation (202 mL) with the postintervention evaluation (282 mL); representing a mean difference of 80 mL or a 40% increase in relation to the initial bladder capacity ($P < .01$; Figure 4A). No difference was observed in the intragroup analysis of the CIC group.

In the intergroup analysis, at 6 months postintervention, the ISRD group presented higher bladder capacity and compliance as compared with those who followed the CIC protocol, with $P = .001$ and $P < .001$, respectively (Figure 4B,C).

TABLE 1 Demographic table according to the group (ISRD and CIC)

Demographic table, group-ISRD vs group-CIC			
	Group-ISRD (n = 90)	Group-CIC (n = 87)	Percentage (%)
Age, y			
5-17	51	40	51%
18-30	17	18	20%
31-43	13	21	19%
44-58	9	8	10%
Education			
High school grade or less	67	59	71%
Some college	17	21	22%
College+	6	7	7%
Race			
White	18	21	22%
Pardo	57	34	51%
Black	24	23	27%
Base pathology			
Myelomeningocele	69	48	66%
Spinal cord trauma	5	7	7%
Guillan-Barré syndrome	3	6	5%
Neuroeschistosomosis	3	4	4%
Bladder exstrophy	2	1	2%
Diabetes mellitus	4	7	6%
Parkinson's disease	1	4	3%
Multiple sclerosis	1	3	2%
HTLV-1 seropositive	2	7	5%
Socioeconomic status			
Medium	8	10	10%
Low	30	38	39%
Very low	52	39	51%
Home			
Rural area	38	29	38%
Urban area	52	58	62%

Abbreviations: CIC, Clean Intermittent Catheterization; ISRD, Intraurethral Self-Retaining Device; HTLV, Human T Lymphotropic Virus.

3.4 | Adverse effects

According to the previous categorization, the intergroup analysis of adverse effects was performed. Among all adverse effects, the ISRD group presented an incidence of 41%, while the CIC group presented with 83% ($P < .01$)

3.5 | Number of daily diapers or daily protectors

Both groups presented a mean use of 7 ± 2 diapers per day at baseline evaluation. At 6 months (intergroup analysis), the ISRD group presented a significant reduction of diaper use with 2 units per day, while CIC group maintained the use of 6 units/day ($P < .01$).

TABLE 2 Postintervention analysis of QOL according to the SF-Qualiveen (ISRD and CIC)

	Intergroup analysis		
Domains	ISRD (n = 90)	CIC (n = 87)	*P* value
Limitation	2 ± 0.70	7 ± 0.67	<.00001
Fear	2.5 ± 1.0	8 ± 0.61	<.00001
Feeling	2 ± 0.71	6 ± 0.98	<.00001
Impact on daily activities	2 ± 0.89	8 ± 0.4	<.00001

Abbreviations: CIC, clean intermittent catheterization; ISRD, intraurethral self-retaining device; QOL, quality of life.

4 | DISCUSSION

CIC represents the main treatment alternative for patients with neurogenic bladder who are unable to perform bladder emptying adequately.[5] However, the practicality of this technique is influenced by a negative impact on QOL, compromising patients' self-esteem.[10]

In this context, ISRD presents advantages as an alternative to CIC, such as the possibility of management as an outpatient procedure both for initial insertion and replacement. Such advantages result in greater autonomy of patients that perform bladder emptying, which significantly affects social interaction. One of the most relevant reports by patients and caregivers was the fact that they could empty their bladders at the precise moment they wanted without having to look for an adequate place to do so. Adults reported how pleasant was the sensation of emptying their bladders at the toilet without anyone's help. This improvement in QOL was reflected by a significant score reduction on the SF-QUALIVEEN questionnaire, both in the intergroup comparison (post-ISRD vs post-CIC moment) and intragroup temporal comparison. Among the reported benefits, adult patients have mentioned resumption of active sexual life without constraints, reduction of social isolation, and increase of autonomy. Child patients have reported reintroduction in school dynamics and the freedom to participate in social activities. The possible placebo effect could not be assessed by the study method.

In relation to the incidence of UTIs, ISRD promoted a reduction in the number of episodes in 6 months. Previous reports have shown that CIC-related UTIs are frequent, with the incidence of 70% to 80%.[13-16] It is important to emphasize that the practicality in the handling of the device also interferes in this outcome, because patients can open

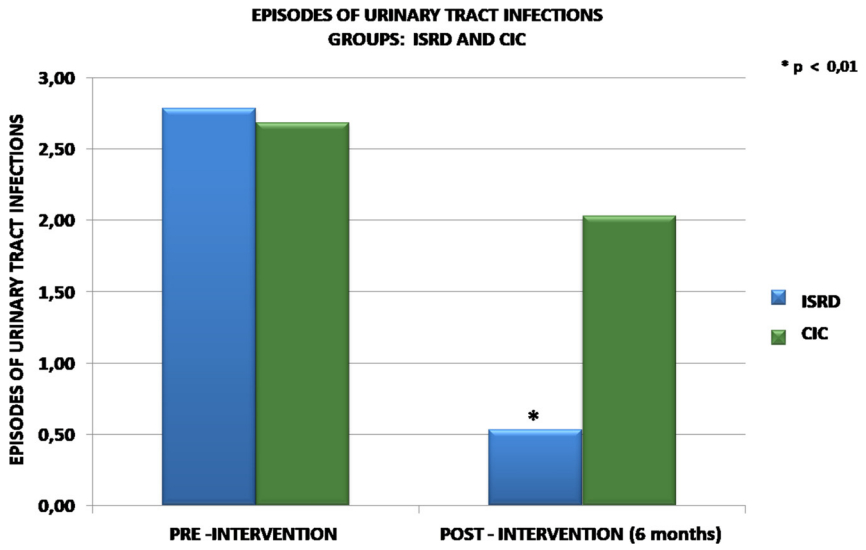

FIGURE 3 Analysis of the number of UTI episodes. CIC, clean intermittent catheterization; ISRD, intraurethral self-retaining device; UTI, urinary tract infection

the device anywhere, while intermittent catheterization requires specific setting and conditions. Our hypothesis is that by reproducing the physiological voiding reducing the accumulation of residue plus raising the frequency of emptying (therefore improving bacterial elimination), the device has promoted this improvement. This benefit may be explained by the directions given for patients how to execute the catheterization.

Regarding urodynamic data, the ISRD presented an expressive gain in bladder capacity and compliance. This can be attributed to mechanisms of distension and contention of the bladder, which are enabled by the attainment of maximum cystometric capacity. This can be explained by the fact that by emptying the bladder at a more appropriate time and not depending on availability of a new catheter and adequate place to perform CIC the bladder tends to behave closer to a normal pattern. Risks of deterioration of upper tracts should not exist because by doing bladder emptying at shorter intervals for the same reasons upper and lower tract tend to behave more physiologically.

These results are in agreement with data from the previous reports that showed bladder capacity gain due to the reduction of urinary loss.[17,18] Experimental studies have also presented an improvement of bladder compliance after detrusor musculature distension.[12,19,20]

The proportion of total adverse events in the ISRD group was approximately half of those found in the CIC group, while more than 50% of the patients in the ISRD group did not present any side effects. This result is in agreement with the data obtained in the pilot study[11] and with previous studies that idealized alternative devices to CIC.[21]

Regarding the number of diapers used daily by subjects, both the ISRD and CIC groups used an average of 7 units per day at baseline evaluation, but only the ISRD promoted a significant reduction after 6 months (2 units per day). This reduction is in disagreement with two recent reports by Jeong et al[22] and Renard et al,[23] in which authors reported no difference in urine leakage and diaper use after the intervention.

In the pilot study conducted by our group,[11] the ISRD demonstrated safety and handling suitability. The present study provides new data that reinforces the ISRD as a viable alternative to intermittent catheterization with significant advantages concerning all analyzed parameters. Future studies with larger populations and longer follow-up may consolidate these findings.

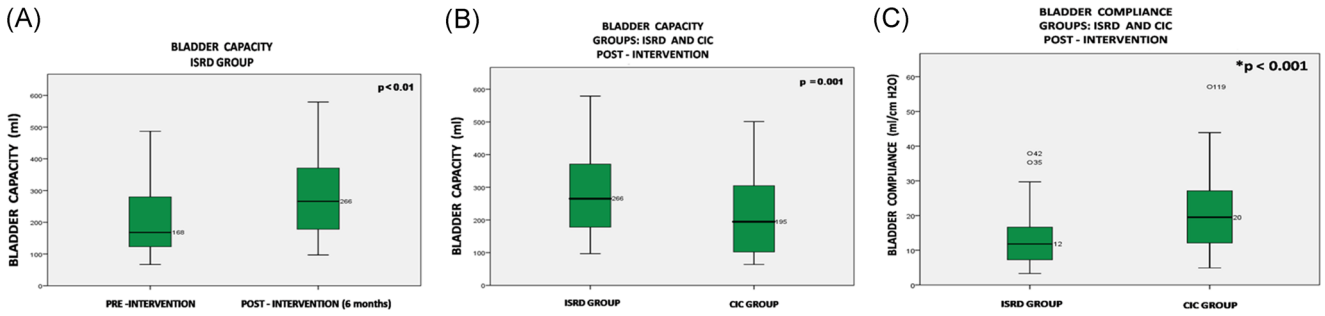

FIGURE 4 A, Intragroup analysis (ISRD) of bladder capacity. B, Intergroup analysis of the bladder capacity. C, Intergroup analysis of the bladder compliance. ISRD, intraurethral self-retaining device

5 | CONCLUSION

The new bladder-draining device (ISRD) has previously shown to be a safe and promising alternative for adequate bladder emptying in female patients. The present study reinforced the safety and ease of handling of the device as well as demonstrated a positive impact on the clinical and psychosocial parameters of the subjects involved.

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