ORIGINAL RESEARCH



Silodosin-induced anejaculation: a promising agent for male oral contraception

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Abstract

Background: The objective of this study was to investigate the feasibility of utilizing silodosin as a non-hormonal, reversible, oral contraceptive for men, alongside elucidating its mechanism of action pertaining to ejaculatory dysfunction. Methods: This is a non-controlled open-label study. Thirty-five sexually active male volunteers, aged between 50 and 70 years and experiencing lower urinary tract symptoms associated with benign prostatic hyperplasia, were administered an 8 mg dose of silodosin. Semen analysis was conducted before and two weeks post-administration of silodosin. To examine sperm in urine, 10 mL samples were obtained via suprapubic bladder aspiration (SBA), with post-ejaculatory urine (PEU) collected from each participant. Additionally, participants completed the IPSS (International Prostate Symptom Score), IIEF (International Index of Erectile Function), and MSHQ (Male Sexual Health Questionnaire Ejaculatory Dysfunction) questionnaires both pre- and post-silodosin treatment. Results: The study involved 35 sexually healthy patients with no prior history of ejaculation complaints who had not previously used silodosin. Of the 33 participants who fulfilled the study requirements, none were able to provide a semen sample. Furthermore, neither SBA nor PEU samples revealed sperm. There was no a prominent decline observed in orgasmic function throughout the duration of silodosin use. Conclusions: Silodosin leads to anejaculation, suggesting its potential as a reliable non-hormonal, reversible and barrier-free oral contraceptive option for men, with minimal impact on orgasmic function.

Keywords

Alpha blockers; Contraception; Anejaculation; Silodosin

Aneyaculación inducida por silodosina: un agente prometedor para la anticoncepción oral masculina

Resumen

Antecedentes: El objetivo de este estudio fue investigar la viabilidad de utilizar silodosina como anticonceptivo oral reversible no hormonal para hombres, además de dilucidar su mecanismo de acción en relación con la disfunción eyaculatoria. **Métodos**: Se trata de un estudio abierto no controlado. Se administró una dosis de 8 mg de silodosina a treinta y cinco voluntarios varones sexualmente activos, de entre 50 y 70 años de edad y que presentaban síntomas del tracto urinario inferior asociados con hiperplasia prostática benigna. Se realizó un análisis de semen antes y dos semanas después de la administración de silodosina. Para examinar los espermatozoides en la orina, se obtuvieron muestras de 10 mL mediante aspiración de la vejiga suprapúbica (SBA), y se recogió orina post-eyaculatoria (PEU) de cada participante. Además, los participantes completaron los cuestionarios IPSS (International Prostate Symptom Score), IIEF (International Index of Erectile Function) y MSHQ (Male Sexual Health Questionnaire Eyaculatory Dysfunction) antes y después del tratamiento con silodosina. **Resultados**: El estudio involucró a 35 pacientes sexualmente sanos sin antecedentes de problemas de eyaculación que no habían usado silodosina anteriormente. De los 33 participantes que cumplieron con los requisitos del estudio, ninguno pudo proporcionar una muestra de semen. Además, ni las muestras de SBA ni de PEU revelaron esperma. No se observó una disminución importante en la función orgásmica durante el uso de silodosina. **Conclusiones**: La silodosina produce aneyaculación, lo que sugiere su potencial como una opción anticonceptiva oral confiable, no hormonal, reversible y sin barreras para hombres, con un impacto mínimo en la función orgásmica.

Palabras Clave

Bloqueadores alfa; Anticoncepción; Aneyaculación; Silodosina

1. Introduction

Ejaculation is a physiological process largely controlled by the autonomic nervous system, consists of two primary phases: emission and expulsion [1]. In the emission phase, closure of the bladder neck effectively prevents retrograde flow of seminal fluid into the bladder. Subsequently, during the expulsion phase, the seminal fluid is expelled [1]. Male condoms and withdrawal represent reversible contraception methods available to men, with typical failure rates of 13% and 20%, respectively [2]. On the other hand, vasectomy, the prevailing surgical option, stands out as the most efficient permanent male contraceptive method in widespread use. However, its irreversible nature and potential for scrotal discomfort often limit its widespread adoption [3]. It has been reported that over 50% of men would consider using a reversible contraceptive method if one were readily available. Additionally, some women express willingness to rely on their partners for contraception [4].

Silodosin is preferred for alleviating lower urinary tract symptoms (LUTS) due to its high α 1A adrenoceptors. Moreover, it is indicated for reducing the duration of stone expulsion in cases of spontaneous passage of lower ureteral stones. Furthermore, individuals experiencing premature ejaculation may derive substantial benefits from silodosin, as it has been shown to markedly enhance intravaginal ejaculation latency time [5]. α 1A-adrenergic receptors (α 1A-ARs) are distributed throughout various anatomical sites, including the prostate, trigone, bladder neck, prostatic capsule and prostatic urethra, where they mediate smooth muscle contraction. Silodosin is employed to alleviate LUTS by antagonizing α 1A-ARs at these locations. However, these receptors are also present in ejaculatory organs such as the seminal vesicles, vas deferens and ejaculatory ducts. Ejaculation is facilitated by vigorous contractions of the accessory sex organs. The sympatholytic effect of silodosin on the smooth muscles of bladder neck and ejaculatory organs may result in ejaculatory difficulties as an adverse outcome [6-8]. The reported incidence of anejaculation following silodosin administration varied significantly, with rates ranging from 19% to 100% [8-16]. In these studies, the dosage of silodosin was predominantly 8 mg, except in the study by Shimizu et al. [13], where a 4 mg dosage was employed. This significant variation may be attributable to differences in how ejaculation rates were assessed, often relying on self-reported questionnaires. In a survey reflecting everyday clinical practice, 71% of participants reported experiencing anejaculation and hypospermia [10]. However, in a smaller study involving 15 healthy male urologists, all of whom were trained to recognize the adverse effects of silodosin, every participant reported complete absence of ejaculation while on the medication [8]. The emergence of ejaculatory problems, such as retrograde ejaculation or anejaculation, remains a subject of ongoing research and lacks definitive elucidation. The α 1-ARs comprise three subtypes α 1A, α 1B and α 1D [17]. Consequently, silodosin's sympatholytic effect on ejaculatory organs may lead to anejaculation. This study aims to examine the ejaculatory dysfunction induced by silodosin and assess the potential for utilizing silodosin as a male contraceptive, given its antagonistic effects on ejaculatory organs.

2. Materials and methods

This is a non-controlled open-label study. Based on the predetermined sample sizes, this study is exploratory in nature. The study involved 35 participants, aged 50 to 70, at our urology and andrology clinic from January 2021 to December 2022. The patients were healthy, sexually active presented with LUTS and were not currently prescribed alpha-blockers. Patients with a history of transurethral prostatectomy and rectopexy, urethral stenosis, obstructive azoospermia, ejaculatory duct obstruction, low semen volume (<1.5 mL), neurological and muscular disorders, concurrent use of medications affecting the autonomic nervous system (including sympathetic, parasympathetic, antiadrenergic and anticholinergic agents), and individuals not meeting the specified age criteria were excluded from the study. Patients were provided with detailed information regarding the efficacy of silodosin and its potential adverse effects.

2.1 Study design

All study participants underwent a diagnostic work-up including a thorough medical history and physical examination, and a digital rectal examination. Urinary tract ultrasound, urinalysis, and uroflowmetry were performed to evaluate LUTS. Biochemical analysis included measurement of serum levels of creatinine, prostate-specific antigen and testosterone. Each patient provided a semen sample. The patients were initiated on a once-daily regimen of 8 mg silodosin. To examine sperm presence in PEU, 10 mL of urine was obtained through SBA, and PEU was obtained from each patient. Additionally, participants completed the IPSS [18], MSHQ [19] and IIEF questionnaires both prior to and two weeks following treatment [20]. After discontinuing silodosin, all participants were assessed for ejaculatory function during a recovery period of approximately one month. Participants provided semen specimens through masturbation into a sterile, specialized container following a three-day period of sexual abstinence for the initial semen analysis. Patients were instructed to consume fluids after ejaculation. Subsequently, patients were monitored for any urge to urinate, and ultrasound examinations were conducted on those reporting sensations of bladder fullness. SBA was carried out on patients with sufficient urine volume in the bladder, and a 10 mL urine sample was collected in a separate container without culture medium. Subsequently, patients were asked to void into a third container to examine the presence of sperm in the PEU.

2.2 Suprapubic bladder aspiration

Experienced urology specialists conducted ultrasound-guided SBA. Bedside ultrasound was employed to assess bladder adequacy for aspiration, identify any anatomical abnormalities, minimize procedural risks, and guide needle insertion. Patients were positioned in the supine position, and bladder visualization was achieved by placing the transducer transversely superior to the pubic symphysis [21]. Bladder volume was then measured, with the total volume serving as a determinant for aspiration [22]. The required bladder fullness for aspiration varied based on individual functional capacity and was determined clinically under ultrasound guidance. The duration for bladder aspiration varied depending on fluid intake and bladder fullness sensitivity. If bladder volume was insufficient for aspiration, the scan was repeated. Once sufficient urine was observed in the bladder, a 10 mL, 0.8×38 mm, $21G \times$ 1 1/2 needle was inserted approximately 1 cm cranial to the public symphysis under direct ultrasound visualization. Upon successful puncture of the anterior bladder wall, 10 mL of urine was aspirated.

2.3 Semen analysis

Semen analysis was conducted by experienced biologists within our andrology laboratory, adhering strictly to the 6th criteria of the 2021 criteria set forth by the World Health Organization (WHO) [23]. The analysis involved assessing semen samples for volume, sperm concentration, motility and morphology. Upon receipt of the semen sample in the andrology laboratory, it was incubated at 37 °C for liquefaction. Subsequently, semen volume was determined gravimetrically, assuming a sperm density of 1 g/mL. The Neubauer hemocytometer was used to count the sperms in both semen and urine.

2.4 Assessment of sperm in the urine

The 10 μ L urine samples obtained from both SBA and PEU were subjected to individual examination for sperm observation. In cases where no sperm were observed, 10 mL of urine from each sample was centrifuged at 3000g for 15 minutes [24].

Subsequently, the analysis was repeated on the pellet, and and a negative result was determined if no sperm were detected. If sperm were observed in both SBA and PEU, retrograde ejaculation was considered. Retained ejaculate was defined as the presence of sperm solely in the PEU sample. Microscopic analyses were conducted using an Olympus BX43 microscope (Olympus, Tokyo, Japan).

2.5 Statistical analysis

The results indicated substantial evidence to reject the assumption of normality. Data are medians unless otherwise stated. To determine the effect of silodosin on urinary symptoms and sexual health, Wilcoxon signed-rank test was conducted and estimated mean differences between IPSS, IEFF and MHSQ scores before and after silodosin treatment were calculated, along with 95% confidence intervals (CIs). A significance level of p < 0.05 was considered statistically significant. Calculated *p*-values were interpreted as descriptive. Statistical calculations were performed using the SPSS software (version 23; IBM, Armonk, NY, USA).

3. Results

Demographic and laboratory characteristics of the patients are presented in Table 1.

All patients initially had normal ejaculatory function and provided a sufficient semen volume. Thirty-three patients completed a two-week course of silodosin treatment and re-

Parameters	Mean \pm SD
Age (yr)	$60.7 \pm 4.5 \ (5070)$
Hypertension (N, %)	
Yes	12 (34%)
No	23 (65%)
Type 2 DM (N, %)	
Yes	6 (17%)
No	29 (82.8%)
Height, cm	172.7 ± 5.2 (164–191)
Weight, kg	79.3 ± 10.8 (62–116)
BMI	$26.5\pm3.1\ (20.436.3)$
PSA, ng/dL	1.3 IQR: 3.4 (4.1–0.6)
Prostate Volume, cm ³	$59.2 \pm 45.6 \ (20 - 280)$
Qmax	$11.9\pm 6.9~(3.135)$
PVR, cm ³	55 ± 45 (10–185)
Testosterone, ng/dL	449.5 IQR: 232 (600–368)
FSH, IU/L	5.45 ± 2.4
LH, IU/L	5.09 ± 2.1
IPSS total (before silodosin treatment)	$20.1 \pm 4.9(6-27)$
IPSS total (after	20.1 ± 4.9 (0 27)
silodosin treatment)	$15.4 \pm 4 \ (5-22)$

N: Number of Subjects; BMI: Body mass index; PSA: Prostate specific antigen; DM: Diabetes Mellitus; Qmax: Maximum flow rate; PVR: Post-voiding residue; FSH: Folliclestimulating hormone; LH: Luteinizing hormone; IPSS: International Prostate Symptom Score; IQR: Interquartile ranges (Q3–Q1); SD: Standard deviation. The results are shown as N (%), mean \pm SD (min–max) (N = 35).

ported an absence of ejaculation. Upon thorough examination, it was observed that these patients had experienced an inability to ejaculate at home during the same period. Four patients exhibited a negligible presence of sperm (1-4 per mL in centrifuged urine) in urine samples obtained through SBA. In two patients, 2-3 sperm were exclusively detected in PEU. However, none of these patients met the diagnostic criteria for retrograde ejaculation; instead, all were classified as experiencing anejaculation. All participants who experienced anejaculation reported a recovery of ejaculatory function following the discontinuation of silodosin. Two participants out of the total 35 enrolled in the study discontinued their participation and silodosin intake two and three days before the scheduled semen analysis, respectively. One of these 2 participants ceased medication two days before, both SBA and PEU samples revealed substantial number of sperm. Conversely, the other participant ejaculated semen, and substantial sperm counts were detected in both SBA and PEU samples.

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Consequently, both subjects received a diagnosis of retrograde ejaculation (Table 2). A Wilcoxon signed-rank test was performed to determine the effect of silodosin therapy on IPSS, IIEF, sexual desire (SD), sexual satisfaction (SS) and MSHQ. Scores were measured before and after drug therapy. The differential points are dispersed approximately symmetrically, as assessed by a histogram with a consecutive normal curve. Changes in the scores of IPSS, IEFF, SD, SS and MSHQ questionnaires were observed before and after treatment with silodosine. Thirty-two of the 35 (91%) participants reported a decrease in IPSS scores, while 3 had no change. However, 34 out of the 35 (97%) patients experienced a decrease in IEFF scores, while only 8 and 10 patients had minimal decreases in SD and SS scores, respectively. Only 1 patient had an increase in CI score. Additionally, the majority of patients reported no change in SD (26) and SS (25) scores. However, all 35 patients experienced a decrease in MSHQ scores. A Wilcoxon signed-rank test revealed a statistically significant difference between the scores before and after silodosin treatment in all

questionnaires (Table 3).

4. Discussion

All patients who completed the two-week course of silodosin were unable to ejaculate. The impact of silodosin on ejaculation was evaluated as anejaculation rather than retrograde ejaculation. The absence of ejaculation in all participants who completed silodosin treatment was regarded as having potential efficacy as an oral contraceptive method for preventing unintended pregnancies in men for the duration of silodosin use. The use of silodosin resulted in a slight decrease in orgasmic satisfaction. However, one patient who had stopped taking silodosin on his own 3 days before the control test experienced ejaculation and provided a semen analysis. This tells us that discontinuation of the drug may lead to a rapid improvement in ejaculation and could lead to unwanted pregnancy, which needs to be investigated. The effects and underlying mechanisms of silodosin on ejaculation have been extensively studied, yet a conclusive consensus remains elusive. While

TABLE 2. Sperm concentration in semen and urine samples.						
Sperm concentration in semen before silodosin						
Semen volume mean \pm SD 3.14 ± 1.47						
Sperm cou	unt (mL) mean \pm S	D		$61.00 \pm 28.02 imes 10^{6}$		
Total sperm count mean \pm SD 175.45 =				$175.45 \pm 115.18 imes 10^{6}$		
Sperm concentration in urine following a two-week course of silodosin						
	Semen	PEU	SBA	Number of patients (N, %)		
	-	+	+	4 (12.12%)		
	—	+	_	2 (6.06%)		
	-	-	-	27 (81.81%)		
Total				33 (100.00%)		
Semen analysis and sperm concentration in urine after discontinuation of silodosin						
	Semen Sperm/mL	PEU Sperm/mL	SBA Sperm/mL	Stopped medication		
1	0	$60 imes 10^6$	$51 imes 10^6$			
2	$50 imes 10^6$	$4 imes 10^6$	$3 imes 10^6$			

PEU: Post-ejaculatory urine; SBA: Suprapubic bladder aspiration; SD: Standard deviation. The results are shown by N(%), +: sperm is present. -: no sperm (N = 35).

FABLE 3.	IPSS, IEFF	and MSHQ	questionnaires	before and	after silodosin.

	Pretreatment (Median)	Posttreatment (Median)	Difference (Median)	Ζ	р	Negative ranks	Positive ranks	Ties
IPSS	20	16	5	-4.959	< 0.0005	0	32	3
IIEF	56	62	-5	-5.154	< 0.0005	1	34	0
SD	8	8	0	-2.309	0.0210	8	1	26
SS	10	10	0	-2.848	0.0040	10	0	25
MSHQ	5	20	-14	-5.220	< 0.0005	35	0	0

IPSS: International prostate symptom score; IIEF: International index of erectile function; SD: Sexual desire; SS: Sexual satisfaction; MSHQ: Male sexual health questionnaire ejaculatory dysfunction. p values are adjusted.

some research suggests silodosin leads to retrograde ejaculation, other claim that its impact on ejaculation presents as anejaculation. Retrograde ejaculation is typically diagnosed based on the observation of 10-15 or more sperm under high magnification in PEU. However, it is possible for ejaculate to remain in the urethra and sperm may still be visible in PEU even after being washed out with urine. Consequently, reliance solely on PEU analysis may be insufficient to distinguish retrograde ejaculation from retained ejaculate in the urethra [25-28]. To address this diagnostic challenge, a comprehensive approach involves examining sperm presence in both urine samples obtained via SBA and PEU [29]. While the presence of sperm in the SBA is diagnostic of retrograde ejaculation, the absence of sperm in the SBA alongside their presence in PEU indicates retained ejaculate. Conversely, the absence of substantial sperm in either the SBA or PEU suggests anejaculation as the likely outcome [30]. Silodosin has been suggested to potentially induce retrograde ejaculation attributed to its relaxant effect on the bladder neck. However, anecdotal patient reports suggest that anejaculation may manifest as a side effect. In a study involving three patients administered 8 mg of silodosin for three days, ejaculation was observed under dynamic Doppler ultrasound visualization [31]. During the procedure, an ultrasound probe was inserted into the rectum, and patients were instructed to ejaculate. Subsequently, seminal fluid leakage into the bladder through the bladder neck was observed. Nevertheless, retrograde leakage may result from ejaculation during rectal probe insertion, possibly affecting bladder neck compliance. The study observed that among 33 patients who completed the course of silodosin treatment and experienced anejaculation, four exhibited a few sperm in SBA and subsequently in PEU. Additionally, in two patients, a few sperm were detected in PEU only. These findings indicate that silodosin administration may infrequently lead to a minimal accumulation of sperm in the prostatic urethra, subsequently leaking into the bladder. However, this was not considered to be retrograde ejaculation. The absence of antegrade ejaculation implies that silodosin inhibits seminal emission by counteracting the contraction of the vas deferens, seminal vesicles, and prostatic ducts [8]. The solitary study examining silodosin's potential as an oral contraceptive for men revealed that its on-demand use before sexual intercourse within a three-hour proved effective in preventing conception. Unlike our study, the participants in this trial, were able to provide semen, but the mean semen volume was 0.68 ± 0.16 mL. No sperm were detected in either the seminal plasma or PEU, attributed to silodosin's alpha 1a antagonistic effect on the vas deferens [14]. However, two patients in our cohort who voluntarily discontinued silodosin and experienced retrograde ejaculation exhibited a lower sperm count obtained via SBA compared to those found in PEU. In patients diagnosed with retrograde ejaculation, it has been reported that the number of sperm leaking into the bladder is always lower than the number of sperm retained in the prostatic urethra [29]. We suggest that the reversal effect of silodosin discontinuation on anejaculation diminishes rapidly, and the relaxing effect on the bladder neck may persist for a few days. Additionally, one of these patients also experienced antegrade ejaculation. The rapid reversal of silodosin's inhibitory effect on ejaculation

raises concerns regarding the potential risk of pregnancy upon drug discontinuation. Further investigations are warranted to elucidate these findings. The on-demand use of silodosin has been associated with reduced complaints of anejaculation [14]. However, studies investigating the impact of silodosin on orgasmic function have yielded conflicting findings. A subjective decline in orgasmic satisfaction was observed in men experiencing anejaculation, and was attributed to weaker contractions of the bulbocavernosus/pelvic floor muscle during ejaculation [13]. Conversely, in healthy individuals, the use of 4 mg/day of silodosin was found to have no discernible effect on orgasmic dysfunction [8]. The findings from animal experiments provide additional support for this observation. In vitro Fertilization studies involving α 1A knockout (KO) or α 1A/B/D triple KO mice demonstrated no alterations in sexual behavior. This aligns with clinical evidence indicating only minimal adverse effects of $\alpha 1$ adrenoreceptor antagonists on libido [32]. In this study, the use of silodosin was associated with a decline in the IIEF score. However, only a small number of patients experienced minimal decreases in the libido-related measures of SD and SS scores. Instances of ejaculatory failure were infrequent among participants, therefore we suggest that the declines in sexual function measures are likely to be due to psychological distress caused by failure to ejaculate. Furthermore, reductions in MSHQ scores also suggest dissatisfaction potentially arising from the inability to ejaculate. A previous study reported similar findings and implications [33]. Despite experiencing complete seminal emission and expulsion, all participants treated with silodosin reported experiencing orgasm. However, 80% of participants reported experiencing discomfort during orgasm, predominantly of mild intensity [33]. The authors of the study concluded that all participants were dissatisfied with the loss of seminal emission. It is essential to emphasize that this study exclusively examined the impact of silodosin on ejaculation, necessitating further investigation to determine its contraceptive efficacy. However, it is worth noting that all participants had no ejaculatory problems prior to enrolment and all who used the drug regularly were unable to ejaculate. Nevertheless, the variation in reported ejaculatory dysfunction rates across studies may be influenced by the use of selfreported questionnaires, which could contribute to the lower observed rates (Table 4, Ref. [8-16]).

This study suggests that a large, multi-centre, controlled trial would be worthwhile. This significant variation may be attributable to differences in how ejaculation rates were assessed, often relying on self-reported questionnaires.

5. Conclusions

Silodosin induces anejaculation rather than retrograde ejaculation, as demonstrated by SBA, a newly developed method for detecting sperm in the bladder. It holds potential as a safe, effective, reversible and non-hormonal alternative for male oral contraception.

	n	Age	Duration of Silosodin use	Anejaculation rate, %
Yokoyama et al. [12] 2011	11	$70.2\pm0.9~(5080)$	1 m	90
Kobayashi et al. [8] 2008	15	32 (26–47)	3 d	100
Sakata et al. [10] 2012	40	$66.9 \pm 6.9 (5584)$	1 m	87
Capogrosso et al. [11] 2015	100	$62.7 \pm 12.8 \ (30 - 88)$	3 m	48
Bhat et al. [14] 2020	63	32.03 ± 2.98	3 h	100
Shimizu et al. [13] 2010	50	30.2 ± 6.5	4 h	62
Sertkaya et al. [15] 2014	129	$63.2 \pm 4.4 (53 76)$	3 m	19
Cihan A et al. [16] 2020	98	59.5 (45-82)	3 m	50
Novara <i>et al.</i> [9] 2014	847	$64.9 \pm 8.0 \ (50 - 87)$	3 m	22

TABLE 4. Studies reporting ejaculatory dysfunction after silodosin use.

n: *number of sexually active patients; d*: *day(s); m*: *month(s); h*: *hour.*

ABBREVIATIONS

SBA, Suprapubic bladder aspiration; PEU, Post-ejaculatory urine; IPSS, International Prostate Symptom Score; IIEF, International Index of Erectile Function; MSHQ, Male Sexual Health Questionnaire Ejaculatory Dysfunction; LUTS, Lower urinary tract symptoms; α 1A-ARs, α 1A-adrenergic receptors; WHO, World Health Organization; CIs, confidence intervals; SD, sexual desire; SS, sexual satisfaction; KO, knockout.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

HU—concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis. HU, BS, MHY, GA, EO, YK—acquisition of data. HU, BS, ED—drafting of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study protocol was approved by (RTEU, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee, 02 March 2023, No: E-40465587-050.01.04-615, 2023/40). Informed consent was obtained from all participants.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Berat Sonmez, Hakkı Uzun, Merve Huner Yigit, Görkem Akça, Eyup Dil, Erdem Orman, *et al.* Silodosin-induced anejaculation: a promising agent for male oral contraception. Revista Internacional de Andrología. 2025; 23(2): 83-89. doi: 10.22514/j.androl.2025.022.