Efficacy of Treatment with Pseudoephedrine in Men with Retrograde Ejaculation

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Abstract:

Objective

To evaluate the efficacy of pseudoephedrine treatment in patients with retrograde ejaculation.

Materials and Methods

Twenty men were medically treated with pseudoephedrine for retrograde ejaculation between January 2010 and May 2016 (12 with complete retrograde ejaculation and 8 with partial retrograde ejaculation). All patients had a semen analysis and post-ejaculatory urinalysis before and after treatment. The treatment protocol consisted of 60 mg of pseudoephedrine every 6 hours on the day before semen analysis and two more 60 mg doses on the day of the semen analysis

Results

Diabetes was the most common etiology for complete retrograde ejaculation (60%), while an idiopathic cause was the most common etiology for partial retrograde ejaculation (82%). Of the 12 complete retrograde ejaculation patients treated with pseudoephedrine prior to semen analysis, 7 (58.3%) recovered sperm in the antegrade ejaculate, with a mean total motile count of 54 ± 20 million. Out of the 8 patients with partial retrograde ejaculation, 5 (62.5%) had a \geq 50% increase in the antegrade total sperm count. The mean total motile count in this group increased from 6.6 ± 3.2 million before treatment to 31.6 ± 13.9 million after treatment, while the percentage of sperm in the urine declined from 41.9 ± 11.2% to 17 ± 10%, respectively (both p < 0.05). Overall, some improvement in seminal parameters occurred in 14 (70%) patients, with 10 patients (38.5% of all patients) achieving antegrade total sperm counts over 39 million.

Conclusion

In men with retrograde ejaculation, a pseudoephedrine regimen prior to ejaculation confers some improvement in ejaculated semen parameters for approximately two thirds of patients and an ejaculated total motile count of greater than 20 million for approximately one third of patients.

Key words: Retrograde ejaculation; Pseudoephedrine; Post-ejaculatory urinalysis; Male infertility

Manuscript:

Introduction:

The mechanism of ejaculation involves a two-fold process of emission and expulsion. In emission, seminal fluid and sperm is delivered from the prostate to the posterior urethra. Sympathetic innervation (T10-L2) facilitates the contraction of the prostate during emission as well as contraction of the bladder neck to prevent retrograde flow of semen. During expulsion, the bulbocavernosus muscle, synchronized with collateral pelvic floor muscles, contract to deliver the ejaculate in an antegrade fashion through the anterior urethra. Somatic innervations (S2-S4) facilitate this this latter process [1].

Failure of expulsion of the emitted seminal content leads to retrograde ejaculation into the bladder. The semen refluxes from the posterior urethra as a result of inadequate bladder neck closure. In complete retrograde ejaculation, no semen is expulsed from the anterior urethra. In partial retrograde ejaculation, a portion of the antegrade emission can be appreciated, and spermatozoa will appear both in the antegrade ejaculate and in the postejaculatory urine. Retrograde ejaculation accounts for up to 2% of all cases of male subfertility [2]. Etiologies of retrograde ejaculation include congenital abnormalities, diabetes, spinal cord injury, bladder neck resection, retroperitoneal lymph node dissection, and of unknown source [3]. Treatment options for retrograde ejaculation include medical management or surgical intervention in order to induce or improve antegrade ejaculation. Alternatively, sperm may be extracted from the urine, to be utilized in assisted reproductive techniques [3].

Clinicians employed both anti-cholinergic and sympathomimetic medications to increase bladder neck tone [3, 4]. The alpha agonist, pseudoephedrine, is one such sympathomimetic, which has been observed to have variable efficacy in the treatment of retrograde ejaculation [5-7]. We aimed to further evaluate the efficacy of pseudoephedrine, with a novel short pseudoephedrine treatment protocol in men with complete or partial retrograde ejaculation.

Materials and Methods:

Institutional review board approval was obtained. A retrospective analysis was performed of a prospectively maintained single-institution male infertility clinic database. Clinic visits ranged from January 2010 until May 2016. All patients were seen by one treating physician (CN). We identified 26 men prescribed pseudoephedrine for the treatment of retrograde ejaculation. These men were diagnosed by a semen analysis and post-ejaculatory urinalysis. Fifteen men had complete retrograde ejaculation as defined by sperm found in post-ejaculatory urinalysis and no antegrade ejaculation, and 11 had partial retrograde ejaculatory urinalysis. Three patients in each group were lost to follow up and did not complete the post-treatment evaluation. Twenty men were treated with pseudoephedrine before providing another semen analysis and post-ejaculatory urinalysis. The indications to treat the patients with partial retrograde ejaculation were a significant percentage of sperm in the urine (≥ 50%) or low sperm counts (< 39 million total sperm count) in the antegrade ejaculate.

We collected data on demographics, medical history, retrograde ejaculation etiology, physical examination, laboratory values and semen analyses, before and after treatment. Patients suspected of having retrograde ejaculation included those with low-volume ejaculate (< 1.5 ml) on the first semen analysis or a history of a known cause for retrograde ejaculation such as retroperitoneal surgery. A diagnostic semen analysis and a subsequent postejaculatory urinalysis were performed. Semen samples were collected by masturbation after 2 to 3 days of sexual abstinence and processed within 1 hour of ejaculation. A post-ejaculatory urinalysis was collected as soon as possible after ejaculation and was examined for the presence of sperm. As retrograde ejaculation patients commonly exhibit low volume antegrade ejaculate, sperm concentration may be misleading. We thus elected to define oligozoospermia as total sperm count less than 39 million according to the 5th percentile of the WHO 2010 reference values [8]. The pseudoephedrine treatment protocol was the same in all patients and included 60 mg every 6 hours the day before semen analysis and two more 60 mg doses on the day of the test in the early morning and 30 to 60 minutes before providing the second semen sample. Hormonal analysis was obtained between 7:00 and 11:00 a.m. by venipuncture and included assays of sex hormone binding globulin, estrogen, albumin, FSH, LH and total testosterone, obtained at the University of Illinois at Chicago laboratory. Testosterone was measured by the quantitative electrochemiluminescent immunoassay. Bioavailable testosterone was calculated according to the Vermeulen formula [9].

Statistical analysis:

Variables are presented as median (interquartile range) or mean ± standard error, as appropriate. A non-parametric Mann-Whitney U test was used to compare complete and partial retrograde ejaculation patient characteristics. A paired Student's t-test estimated the significance of change in the semen analyses and post-ejaculatory urinalyses with treatment.

Statistical tests were two-sided and were considered statistically significant with p < 0.05. Analyses were performed with IBM SPSS statistics[®], version 20.

Results:

The median age at presentation was 36 (31.5, 41). Approximately two thirds of the patients had primary infertility and a third were evaluated for secondary infertility. The most common etiologies were idiopathic (46.2%) and diabetes mellitus (34.6%), but these varied significantly between patients with complete retrograde ejaculation and partial retrograde ejaculation (Table 1). Testicular longitudinal axis and hormonal analyses were not significantly different between the groups (all p > 0.05).

Men with complete retrograde ejaculation had an average of 83 ± 20.7 million sperm in the post-ejaculatory urinalysis at presentation. Out of the 12 patients with complete retrograde ejaculation treated with pseudoephedrine prior to semen analysis, 7 (58.3%) had sperm recovered in the antegrade ejaculate, with a mean total sperm count of 273.5 ± 172.5 million and a mean total motile count of 54.1 ± 20.5 million. The sperm count in 5 of these 7 responders improved to > 39 million, while 2 achieved an antegrade count in the oligozoospermia range.

Seven (87.5%) of the 8 patients with partial retrograde ejaculation treated with pseudoephedrine had improvement in the semen parameters of the post-treatment semen analysis. Five had a greater than 50% increase in the total sperm count. The mean total sperm count in this group increased from 26.9 ± 8.5 million before treatment to 84.2 ± 24.6 million after treatment, while the percentage of sperm in the urine declined from $41.9 \pm 11.2\%$ to $17 \pm 10\%$, respectively (both p < 0.05). Treatment was not observed to change sperm motility or total motile count significantly.

Overall, improvement in seminal parameters occurred in 14 (70%) patients, with 10 patients (38.5% of all patients) achieving antegrade total sperm counts over 39 million.

Discussion:

Clinicians have employed a variety of sympathomimetic and anticholinergic drugs alone and in combination to induce antegrade ejaculation in men with retrograde ejaculation. Two recent systematic reviews addressed the issue of medical treatment for retrograde ejaculation [3, 7]. The majority of the studies included in these two review articles were case reports or very small case series. Studies varied by etiology of retrograde ejaculation and methods of treatment including type of medication and length of treatment, and the results varied accordingly. In a systematic review of the literature performed from August 2008 to April 2009 including 9 papers, Jefferys et al. [3] reported an overall antegrade ejaculation rate of 22% in men treated with anticholinergics, 28% in men treated with sympathomimetics, and 39% in men receiving a combination of these drugs. However, higher success rates have also been reported. Ochsenkuhn et al. [10] treated 11 patients with retrograde ejaculation with 7 having complete and 4 having partial forms and a history of retroperitoneal surgery. These investigators reported achieving antegrade ejaculation and improved semen parameters in all patients by prescribing imipramine for a week before ejaculation.

Pseudoephidrine is an α -adrenergic agonist that may be used to treat men with retrograde ejaculation. It is readily absorbed from the gastrointestinal tract with a short onset of action and has a half-life of about 5-8 hours [11]. The maximum recommended dose is 240 mg each day. Sympathomimetic adverse events include various degrees of dizziness, sleep disturbances, weakness, restlessness, dry mouth, nausea and sweating, and these occur frequently in patients that respond to therapy [4]. We chose to study pseudoephedrine, as it is a commonly used medication for indications such as the common cold, it is generally regarded as safe, and its adverse reaction profile is considered milder than other alternative medications [4, 5, 12, 13]. We based our treatment protocol on its favorable pharmacodynamics.

Few studies address the efficacy of pseudoephedrine for the treatment of retrograde ejaculation [4]. Pseudoephedrine was reported to induce antegrade ejaculation in only 1 out of 7 men with a history of retroperitoneal lymph node dissection [14]. In this study observing a low response rate, the researchers prescribed pseudoephedrine at a relatively low dose of 24 mg daily for two weeks before ejaculation. Hsiao et al. successfully achieved antegrade ejaculation in 2 out of 4 patients after retroperitoneal lymph node dissection prescribing a dose of 60 mg four times daily for 2 days before ejaculation. Encouraging results were described by Arafa et al [5] in diabetic men with retrograde ejaculation (23 complete and 10 partial). They prescribed three different courses of medical treatment with imipramine 25 mg twice daily, pseudoephidrine 120 mg twice daily, or combination of the two drugs, achieving antegrade ejaculation in 38.5%, 47.8%, and 61.5% of patients, respectively. Our results using pseudoephidrine in a group of patients with mixed etiology are comparable to those of the latter study, producing approximately 60% of antegrade ejaculation in men with complete retrograde ejaculation.

The length of treatment is another area of controversy in the literature. Researchers employed variable durations of treatment including two days [6], four days [15], and 2 weeks [5]. A consensus group of highly experienced urologists [16] recommended prescribing sympathomimetics for 7 days before ovulation or the anticipated time of a semen sample. Our data suggests that approximately 30 hours of treatment may be sufficient to achieve comparable results. A prospective randomized comparative study is required in order to more definitively address the optimal duration of treatment.

Our study evaluated men presenting for infertility evaluation to a referral andrology clinic. We could not identify an etiology in approximately 50% of the patients presenting with retrograde ejaculation. The majority of these patients (9 of 12) had partial retrograde ejaculation. These patients with idiopathic retrograde ejaculation seem to respond well to

pseudoephedrine treatment. While the diagnosis of complete retrograde ejaculation is evident by laboratory findings, the definition of partial retrograde ejaculation is controversial and illdefined. Finding greater than 10–15 sperm per high power field in post-ejaculatory urinalysis was traditionally considered diagnostic of retrograde ejaculation [17]. However, healthy and fertile men may have sperm observed in the post-ejaculatory urinalysis [18, 19]. Engelbertz et al. [20] discovered spermatozoa in the post-ejaculatory urinalysis of 60-70% of healthy volunteers, examined at various times up to 5 hours after ejaculation. Sivananthan et al. [21] revealed sperm in the post-ejaculatory urinalysis in all 11 healthy men examined, and sperm were more likely to be present in the first fractions of the collected urine. Mehta and colleagues [18] demonstrated that the majority of the sperm are found in the first portion of the voided urine. Thus, it was suggested by many researchers that a common cause of a positive post-ejaculatory urinalysis is retained semen in the urethra rather than true retrograde ejaculation. Spermaturia may also appear after extended periods of sexual abstinence [22], although this is unlikely in men attempting to conceive. Sigman et al. [19] observed that both fertile and subfertile men had similar amounts in both the absolute quantity and the percentage of sperm in the urine, but less than 10% of the fertile control group had more than 50% of the total sperm in the urine, and none had more than 80%. These investigators suggested that defining a positive post-ejaculatory urinalysis by a threshold of the percentage of total sperm present in the urine may best identify men with ejaculatory dysfunction. A more recent definition proposed that if the number of sperm in the urine nears or exceeds that in the antegrade specimen at approximately 50% or more, retrograde ejaculation is considered clinically significant [23]. Nonetheless, these definitions do not account for variability in sperm concentration and total motile count nor the possible toxic effects of urine to sperm [24]. For example, is a partial retrograde ejaculation of 60% in a man with a total count of 300 million sperm more clinically significant than a retrograde ejaculation of 30% in a man with a total count of 10 million sperm? The literature is conflicting, and other researchers did not find a significant amount of sperm in the post-ejaculatory urinalysis of healthy controls. Fedder et al. [25] compared 26 men with diabetes to 16 controls and observed all men in the control arm to have less than 1 million sperm in the post-ejaculatory urinalysis. As our results show, many men lack a clear etiology supporting anatomic or physiological ejaculatory dysfunction. We elected to treat patients with partial retrograde ejaculation who were likely to have verifiable ejaculatory dysfunction and that may benefit from therapy. Consequently, we prescribed pseudoephedrine to patients with a high percentage of the total sperm count in the urine or with low sperm counts. Most of these patients demonstrated higher total counts in the antegrade ejaculate and lower percentage of sperm in the urine following treatment with pseudoephedrine.

Our study shares similar limitations with previous studies of therapy for retrograde ejaculation. Ours was a retrospective uncontrolled study with a limited cohort size and consequently of limited statistical power and subject to selection bias. Another limitation includes the primary endpoint being improvement in semen parameters rather than pregnancy rates or live births rates. Despite its limitations, the present study adds to a small but growing body of knowledge in an understudied area on pseudoephedrine use for the treatment of retrograde ejaculation. Our results suggest that pseudoephedrine is an effective treatment for retrograde ejaculation with beneficial effects in approximately two thirds of patients. We propose that a shorter duration of treatment may be sufficient to achieve a beneficial effect comparable with longer treatment regimens prone to adverse effects of sympathomimetic agents. Future preferably multi-center prospective randomized studies studies are encouraged to further elucidate the optimal treatment regimen.

Conclusions:

Pseudoephedrine treatment is beneficial in approximately two thirds of selected patients with retrograde ejaculation. A third of patients will achieve normozoospermia, defined as sperm count \geq 39 million. The described protocol of pseudoephedrine treatment before ejaculation may have comparable results with longer treatment protocols.

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Table 1: Patients' characteristics and follow up

Variable	Complete retrograde ejaculation	Partial retrograde ejaculation	Overall
	N = 15	N = 11	N = 26
Age at presentation, years, median (IQR)	34 (30, 39)	39 (35, 42)	36 (31.5, 41)
Primary vs. Secondary infertility, n / n	9 / 6	8/3	17 / 9
Etiology			
Diabetes Mellitus, n (%)	9 (60%) *	0	9 (34.6%)
Retroperitoneal surgery, n (%)	2 (13.3%)	1 (9%)	3 (11.5%)
Other, n (%)	2 (13.3%) *	1 (9%)	3 (11.5%)
Idiopathic, n (%)	3 (20%)	9 (82%)	12 (46.2%)
Testicular longitudinal axis			
Right, mean ± s.e.	4.68 ± 0.16	4.62 ± 0.28	4.65 ± 0.15
Left, mean ± s.e.	4.79 ± 0.12	4.58 ± 0.29	4.71 ± 0.14
Hormones			
LH, IU/L, mean \pm s.e.	4.67 ± 0.64	3.48 ± 0.33	4.10 ± 0.38
FSH, IU/L, mean ± s.e.	4.65 ± 0.84	5.72 ± 0.85	5.19 ± 0.59
Total testosterone, ng/dL, mean ± s.e.	474.8 ± 51.8	375.6 ± 46.1	429.3 ± 35.9
Bioavailable testosterone, ng/dL, mean ± s.e.	216.3 ± 22.6	193.4 ± 19.4	205.9 ± 15
Lost to follow up, n	3	3	6

* One patient had both diabetes mellitus and a history of transurethral resection of the midline cyst as possible etiologies for his retrograde ejaculation. Consequently, percentages do not add to 100%.

** Other etiologies include Prune belly syndrome and transurethral resection of the midline cyst in the complete retrograde ejaculation group, and multiple medications (clonidine, bupropion, thioridazine) in the partial retrograde ejaculation group.

Table 2: Semen parameters before and after treatment with pseudoephedrine

	Complete retrograde ejaculation (treatment responders only)		Partial retrograde ejaculation			
Variable	N = 7		N = 8			
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Р	
Ejaculate volume, ml	0	1.19 ± 0.46	0.70 ± 0.16	1.03 ± 0.18	< 0.05	
Total sperm count in ejaculate, millions	0	273.5 ± 172.5	26.9 ± 8.5	84.2 ± 24.6	< 0.05	
Percentage of total sperm in urine, %	100	39 ± 16.9	41.9 ± 11.2	17 ± 10	< 0.05	
Total motility, %	0	32.3 ± 6.3	25.7 ± 8.7	31.6 ± 7.4	NS	
Total motile count in ejaculate, millions	0	54.1 ± 20.5	6.6 ± 3.2	31.6 ± 13.9	NS	
Oligozoospermic (sperm count < 39 million), n	N/A	1	7	3	NS	
Normozoospermic (sperm count ≥ 39 million), n	N/A	6	1	5	NS	