Research article

Midodrine in patients with spinal cord injury and anejaculation: A double-blind randomized placebo-controlled pilot study

Bernard E. Leduc¹, Christine Fournier¹, Géraldine Jacquemin¹, Yves Lepage², Bernard Vinet³, Pierre-Olivier Héту³, Miguel Chagnon²

¹Department of Rehabilitation Medicine, Institut de réadaptation Gingras-Lindsay-de Montréal, Montréal, Canada,

²Department of Mathematics and Statistics, Université de Montréal, Montréal, Canada, ³Department of Biochemistry, Hôpital Notre-Dame du Centre Hospitalier de l'Université de Montréal, Montréal, Canada

Objective: The objective of this study is to evaluate the efficacy of midodrine in the treatment of anejaculation in men with spinal cord injury (SCI).

Study design: Prospective, double-blind, randomized, placebo-controlled pilot study.

Method: Men with anejaculation associated with SCI (level of injury above T10) of more than 1 year in duration were approached. Those with no ejaculatory response to one penile vibratory stimulation (PVS) trial were assigned in a double-blind manner to one of the two following interventions once a week for a maximum of 3 weeks or until ejaculation occurred: oral administration of flexible midodrine (7.5–22.5 mg max) followed by PVS (group M), or oral administration of flexible sham-midodrine (placebo) followed by PVS (group P). Sociodemographic data, medical characteristics, and plasma desglymidodrine concentration were collected for all participants.

Outcome measure: Ejaculation success rate in each group.

Results: Among the 78 men approached, 23 participants (level of SCI: C4–T9) were randomized. Three participants abandoned the study and 20 completed the study; 10 were assigned to group M, 10 to group P. Ejaculation was reached for one participant of group M and for two participants of group P. Autonomic dysreflexia associated to PVS occurred in three patients.

Conclusion: In this small sample study, treatment of anejaculation after SCI with midodrine and PVS did not result in a better rate of antegrade ejaculation in 10 men than in 10 men treated with a placebo and PVS.

Keywords: Anejaculation, Midodrine, Spinal cord injury

Introduction

Anejaculation is frequently related to the consequences of traumatic spinal cord injury (SCI) occurring in men.¹ In the absence of antegrade ejaculation obtained either by self-stimulation, or during sexual relations, the proposed interventions to reach ejaculation usually include penile vibratory stimulation (PVS)² or, if this fails, and particularly for fertility purposes, electroejaculation by rectal stimulation.³ A pharmacological approach is also described, inspired by the treatment of anejaculation in men without SCI, based mainly on

the use of sympathomimetic agents and in particular midodrine chlorhydrate.^{4,5} Observational studies (case series) of men with SCI and anejaculation treated with oral midodrine and PVS report an antegrade and retrograde ejaculation success rate ranging from 16 to 50%, and up to 44% for antegrade ejaculation alone.^{6–9} To date, to the best of our knowledge, there has not been a randomized placebo-controlled trial to evaluate the efficacy of midodrine for ejaculatory dysfunction in men with SCI. Surveys of those with an SCI indicate that improvement in sexual function, and in particular their ability to obtain antegrade ejaculation, remains a priority to improve their quality of life or for fertility purposes.¹⁰ Thus, any medical recommendation, based on convincing data in favor of improvement of

Correspondence to: Bernard E. Leduc, Department of Rehabilitation Medicine, Institut de réadaptation Gingras-Lindsay-de Montréal, 6300 Darlington Avenue, Montreal, QC, Canada H3S 2J4.
Email: leduc_51@sympatico.ca

ejaculatory function, would be welcomed by men with SCI and the absence of antegrade ejaculation.

The purpose of this study is therefore to evaluate the efficacy of midodrine for the treatment of antegrade anejaculation in men with SCI. Contrary to other studies meant to evaluate the total ejaculatory response (antegrade and retrograde ejaculation), only antegrade ejaculation was considered for this study, essentially because many men with SCI who are unable to ejaculate during intercourse expressed frequently their wish to recover or improve the antegrade ejaculation, without taking into account the retrograde ejaculation.

Method

Study design

This is a prospective, randomized, placebo-controlled, double-blind study. The main outcome measured was the ejaculation success rate among treated subjects.

Participants

The study project was posted on the site of three rehabilitation centers in the Montréal area. Subjects interested in participating in the study made an appointment with one of the physician authors (B.E.L., C.F., G.J.) at the outpatient clinic of the IRGLM. Participants had to meet the following inclusion criteria: ≥ 18 years of age, traumatic SCI of at least one year duration, the absence of ejaculation since at least one year after SCI, and the level of the neurological lesion above T10. The exclusion criteria were: use of midodrine or alpha-adrenergic receptor antagonists, medical condition which contraindicates the use of midodrine or a penile vibratory stimulator (local wound or infection, uncontrollable autonomic dysreflexia (AD) during previous PVS tests), previous sexual dysfunction, associated medical condition likely to cause sexual dysfunction, such as hypertension and depression, managed with drugs known to have secondary effects on sexual function. Patients treated with baclofen, also known for its possible side effects on sexual function, were not excluded because of its frequent use in people with SCI. Usage of baclofen was however documented for participants of both groups.

The following data were gathered for each patient: age, weight, level and severity of the SCI according to the *American Spinal Injury Association* (ASIA) Impairment Scale (AIS),¹¹ duration of the SCI (time since injury), the presence or absence of the bulbocavernosus reflex, and the withdrawal reflex of hip flexors upon scratching the sole of the feet (the presence of these reflexes is associated with ejaculation induced by

PVS).¹² Side effects occurring during the study were noted.

Protocol

After the bladder was emptied, an initial PVS test (Ferti Care, Multicept, Albertslund, Denmark), conducted by a nursing staff member at the outpatient clinic, allowed participants who did not reach ejaculation by this procedure to be eligible for subsequent randomization. For those with an SCI $\geq$ T6, a prescription of nifedipine (10 mg) before the PVS was recommended to prevent an episode of AD.¹³ The vibrator head was placed on the frenulum of the penis. It could be moved to the glans penis and sometimes also on the shaft of the penis if no ejaculation was obtained. Under regular monitoring of vital signs and inspection of the penile skin, the session continued for a maximum duration of 3 minutes at a time (maximum of five periods of stimulation if no ejaculation). Stimulation parameters were set initially at a frequency of 100 Hz and amplitude of 2.5 mm. If no ejaculation occurred after three cycles of PVS, individual adjustments of stimulation parameters were provided during the next stimulation cycles, by increasing the peak-to-peak amplitude of the device up to 3.5 mm and/or increasing the frequency above 100 Hz. Those patients who ejaculated during the PVS procedure were excluded for the rest of the study. Only non-responders to PVS were then randomly assigned to one of the following two groups according to a random computer number generator: oral midodrine followed 1 hour later by PVS (group M), or oral placebo which looked identical to the midodrine tablets, followed 1 hour later by PVS (group P). The 1-hour period between taking the drug and the PVS corresponds to the average time that the active metabolite of midodrine, desglymidodrine (DGM), takes to reach maximum concentration.¹⁴

For both groups, the study was double-blinded with the drug taken (midodrine or placebo) once per week according to a progressive dose, spread out over 3 weeks if no ejaculation occurred during the study. In the event of ejaculation during a visit, the subject's participation was ended at this stage.

The dose of midodrine used on the first visit was 7.5 mg. If no ejaculation occurred during the first visit, the participant was asked to come in 1 week later for a second dose, depending on the groups, of 15 mg of midodrine or the placebo, followed 1 hour later by PVS and finally, in the absence of ejaculation during this second visit, a final meeting was conducted the following week for a third dose, depending on the groups, of 22.5 mg of midodrine or the placebo followed by

PVS. The rate of antegrade ejaculation was measured in each of the groups, without seeking the presence of retrograde ejaculation or the presence of spermatozooids in the ejaculate.

A blood sample to measure the plasma DGM level (ng/ml) by high-performance liquid chromatography was done on the day of ejaculation, or, in the absence of ejaculation, at the participant's final visit.

Statistical analysis

Both groups of participants were characterized according to the different variables measured and recorded using descriptive statistics and frequency tables. A comparison of the averages between the two groups (M and P) was done using a Student's *t*-test for independent samples for the continuous variables (age, duration, weight, and maximum oral dose), whereas the distribution of the frequencies of the discrete variable frequencies (severity of the SCI, the presence of the bulbocavernosus reflex, hip flexion reflex, the number of trials and ejaculation) was compared between the two groups using Fisher's exact test. The characteristics of the 20 participants, considered all together, was compared to those of the participants who abandoned the study (group A). The same statistical procedures as for the comparison between groups P and M were used for the comparison between groups A and [P + M] who withdrew after having given their consent.

For the blood pressure (BP) measures, (diastolic and systolic), the averages were compared between the groups and observation times (pre-post) using a two-factor analysis of variance in which one of the factor is repeated: one two-level group factor (midodrine and placebo) and one repeated time factor (pre and post).

The Pearson correlation coefficient was also used to measure the linear relationship between the continuous variables: plasma DGM and weight of the participants.

Analysis were done with SPSS version 21 at the significance levels were set at 5% ($P < 0.05$).

Results

Participant characteristics

The participant recruitment process was spread over 4 years to accumulate the 20 randomized subjects who completed the study (Fig. 1).

The characteristics of each group, with no significant differences noted between them, had levels of SCI ranging from C4 to T9 (Table 1).

Comparison between the group of 9 subjects who abandoned the study (i.e. 6 subjects eligible for

randomization who abandoned before being randomized and 3 participants who had been randomized) and all 20 participants (group M + group P) who completed the study showed no significant difference between them for age, severity of the SCI, weight, and the presence of bulbocavernosus and hip flexion reflexes. However, the average (8.4 years) duration of the SCI of group P + M (one value of which was 34 years for one subject) is significantly higher than that (3 years) of group A ($P = 0.024$).

Nifedipine, as a preventive medication of AD, was administered before the PVS procedure to 11 patients with a lesion at $\geq T6$, 5 in the control group (P) and 6 in the midodrine group (M). Altogether, 14 participants were treated with baclofen at the time of the study, 7 in each group.

Ejaculatory response

Only one participant (10%) from group M reached ejaculation while two participants (20%) from group P reached ejaculation. In group M, the 56-year-old participant with a T5 ASIA SCI had not ejaculated for 3 years. In group P, one 21-year-old participant with a T7 ASIA B SCI had not ejaculated for 5 years, and a second participant (C7 ASIA C) had not ejaculated for 4 years. The characteristics of these participants did not differ clinically from those of other participants in their group.

Adverse effects

Three patients whose level of injury was rostral to T6 (none of whom ejaculated, two in group M and one in group P), presented an episode of AD during PVS. This was quickly resolved by stopping the procedure. It is to be noted that two of these three participants had refused to take the nifedipine tablet before the procedure.

Average baseline BP values, diastolic and systolic, were not significantly different between the two groups before taking midodrine or the placebo. A significant average increase of 16.2 mm was observed in systolic BP for the group M 1 hour after taking midodrine ($P < 0.001$) but no significant difference for group P ($P = 0.759$); the average systolic BP for group M became significantly higher than that of group P ($P = 0.007$) after taking midodrine. The average diastolic BP of the subjects in group M rose significantly to 8.7 mm 1 hour after taking midodrine ($P = 0.001$) but no significant difference was observed in group P ($P = 0.739$); the average diastolic BP of group M became significantly higher than that of group P ($P = 0.010$) after taking midodrine. Except for the three cases of AD,

Figure 1 Flow chart of study population.

this slight rise in BP was not accompanied by any particular symptom (headache, dizziness). Finally, no penile skin lesion appeared following application of the penile vibrator.

Plasma DGM

In group M, plasma measurement of DGM, performed on only seven participants, since three samples were lost, reached 87.9 ± 34.1 ng/ml (range: 43.2–140.2). Correlation between the plasma DGM and the weight of the participants proved to be non-significant ($P = 0.895$). In addition, the plasma concentration of DGM of the only participant of group M who ejaculated was not particularly high, being near the average value measured in the group. Since only three participants

reached ejaculation, no statistical analysis was undertaken to seek any association between plasma DGM concentration and ejaculation success rate.

Discussion

This placebo-controlled double-blind study sought to evaluate the efficacy of midodrine on ejaculation success rate in men with SCI and antegrade anejaculation. Definitive conclusions cannot be drawn because of the small number of participants to complete the study.

The difficulty of recruitment to obtain a sample of sufficient size could raise certain factors, including poor interest from several patients approached with regard to the purpose of the study and the logistical

Table 1 Comparison between midodrine and control groups according to characteristics

	Midodrine + PVS N = 10	Placebo + PVS N = 10	P value
Age (years)*	42.2 ± 10	36.2 ± 11.9	0.23
Time since injury (years)*	9.15 ± 11.3	7.65 ± 8.1	0.73
Weight (kg)*	82.8 ± 12.1	76.23 ± 17.8	0.34
Severity of injury (n)			
C1–4 AIS A, B, C	5	2	0.10
C5–8 AIS A, B, C	5	4	
T1–S5 AIS A, B	0	4	
Any level AIS D	0	0	
HR (n)	5	2	0.35
BCR (n)	7	9	0.58

*Values expressed as means ± SD.

SCI, spinal cord injury; AIS, American Spinal Injury Association (ASIA) Impairment Scale; HR, hip flexion response; BCR, bulbocavernosus response.

requirements of the protocol which could seem restrictive (the number and duration of visits). Also, in compliance with the ethical standards of the research concerning participant recruitment, the treating physicians (*authors*) did not perform the recruitment themselves. Finally, according to the design of the study, the possibility of having to take a placebo rather than midodrine contributed, according to some candidates, to a disinterest in the project. Faced with this report, and in the eventuality of another placebo-controlled study project addressing the same topic, a multicenter study would probably have a better chance of attaining a larger and sufficient sample on the statistical level.

The ejaculation success rate observed in both groups is very low in relation to that recorded in the case series (midodrine followed by PVS) mentioned in the introduction. The reasons for the low ejaculation rate are uncertain, but could hypothetically be due to various causes. Definition of level of injury >T10 as an inclusion criterion is based on the site of the ejaculatory spinal cord centers, located below T10 level and presumably spared by the neurological lesion, and therefore still functional, thus making it possible to reach ejaculation triggered by PVS. However, contrary to the relative ease of determining clinically the upper limit of the neurological injury (the level of SCI according to ASIA),¹¹ it is more difficult to clinically determine the caudal extension of the SCI and thus, the lower limit of the injury in the spinal cord. This suggests that a certain number of patients with a thoracic SCI level >T10 (10 in our sample) could have caudal extension beyond the T10 spinal cord segment, and thus have compromised reflex ejaculatory capacity in response to midodrine as well as to PVS.

The bulbocavernosus and hip flexor response (which are usually predictive factors for a response to PVS) were found in the majority of participants.¹² The absence of these factors are therefore not the reason for the low ejaculation rate in our patients.

The PVS trials were conducted according to the recommended standards. These standards entail variations in the stimulation parameters. These adjustments are individualized and thus vary between participants tested and according to the experience of people handling the penile vibrator. These variations in PVS application may be more important than they appear at first glance when PVS-triggered ejaculation success rate is considered.

Midodrine, the prodrug of DGM, an adrenergic alpha-1 receptor agonist used mainly to treat subjects with low BP, can also stimulate the smooth muscles of the structures involved in the emission of sperm and can contribute to some control of retrograde ejaculation (closure of the bladder neck).¹⁵ It is thought to promote antegrade ejaculation more effectively than other sympathomimetic substances⁴ and act as a modulator of the activity of the spinal pattern generator for ejaculation.¹⁶ Maximal dose of midodrine used was 22.5 mg instead of higher doses up to 30 mg (men with paraplegia),⁶ which may induce significant increase of BP. Our choice was to limit the occurrence of adverse side effects, knowing that the average dose of midodrine for achieving ejaculation in Soler's study was 17.8 ± 6.9 mg.⁶ The possibility that ejaculation could have occurred in some patients of group M, had they received a higher dose than 22.5 mg, is to be noted.

It may be difficult to clearly separate the respective roles of midodrine and PVS, at the root of an ejaculatory response in patients treated by this combined procedure; an alternative to this approach, with the purpose of a better evaluation of the efficacy of midodrine alone, could involve its daily oral administration for 1–3 months. Antegrade ejaculation success rate during sexual activity would then be the main measured outcome.⁵ This could make interpretation of the results easier by not having to consider the possible contribution of PVS if it had been combined with midodrine as reported in the majority of case series using this approach.

Finally, we do not think that use of nifedipine in some patients would have affected the results by decreasing the potential for ejaculation. Nifedipine, a calcium ion influx inhibitor (channel blocker), selectively acting in cell membranes of vascular smooth muscle and cardiac muscle has no effects on the urogenital system

muscle cells or central and peripheral neural pathways, involved in the ejaculatory reflex.

This study has some limitations. The small size of the sample does not allow us to draw any significant conclusions. For this study, PVS failure was defined after one trial of PVS only; definition of PVS failure after two consecutive trials of PVS instead of only one trial and proceeding to PVS with two vibrators^{17,18} could have modified the final number of non-responders to PVS eligible for randomization. Plasma DGM was not measured in three samples from group M; considering the wide range of measured values, we do not think that the missing data would have made a significant change to the interpretation of the results. Somatic responses below the level of SCI during PVS trials were not specifically documented, hence their correlation with an ejaculatory response was not done.

Conclusion

In this pilot study with a small sample size, treatment of anejaculation after SCI did not result in a better rate of antegrade ejaculation in 10 men treated with midodrine and PVS than in 10 men treated with a placebo and PVS. Further randomized placebo-controlled trials with a larger sample size are required for better evaluation of the efficacy of midodrine on anejaculation in men with SCI.

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Disclaimer statements

Contributors All authors played a role in writing the manuscript and approved the version to be published. BEL, CF and GJ conducted the trial and wrote the paper. YL and MC contributed mainly to the study design, analysis, and interpretation of the data, and critical revision of the manuscript. POH and BV contributed mainly to acquisition and analysis (Laboratory) of data and revision of the manuscript.

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Conflict of interest None.

Ethics approval Ethical approval for this study was received from the following institution: Institut de réadaptation Gingras-Lindsay-de-Montréal.

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