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JSM Sexual Medicine

Research Article

Efficacy and Safety of Etilefrine as Priapism Prophylaxis in Patients Submitted to Penile Dynamic Colour Doppler Ultrasonography: A Retrospective Study on 750 Prospectively Collected Patients

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Submitted: 29 June 2020

Accepted: 30 July 2020

Published: 06 August 2020

ISSN: 2578-3718

Keywords
- Penile Color Doppler US
- Priapism
- Medical treatment
- Penis diagnostic imaging
- Prostaglandis
- Adverse effects

Abstract

Introduction: Dynamic Penile Colour Doppler Ultrasound (DPCDU) is currently regarded as a second-level diagnostic test in patients with Erectile Dysfunction (ED), of which a vasculogenic aetiology is suspected. The intracavernosus injection of vasodilators agent during the exam can be responsible of prolonged erection and priapism in 1-10% of patients depending on the pharmacological stimulation adopted and thus various sympathomimetic drugs have been used to prevent this side effect.

Aim: To evaluate the effects of intracavernous injection of etilefrine administered at different dosages, in terms of detumescence achievement and onset of adverse events in patients undergoing Penile Dynamic Colour Doppler ultrasonography with intracavernous PGE1.

Methods: We performed a retrospective analysis on 750 patients, divided in 3 groups, treated with etilefrine as priapism prevention after DPCDU with PGE1. Group 1 (150 patients) was treated with etilefrine 10 mg; Group 2 (300 patients) with etilefrine 5 mg; Group 3 (300 patients) with etilefrine 3 mg. All patients' cardiac rhythm and blood pressure were monitored at 5, 15, 30 and 60 minutes, and pain at injection site was recorded when reported. Clinical history of the patients with regards to andrological, psychological disorders and overall comorbidities was also considered.

Results: All groups reported a 100% rate of success in priapism prevention after administration of etilefrine, independently of the dosing. Side-effects were infrequent, mild and self-limiting: the highest incidence was in Group 1 with a 5.3% incidence of haemodynamic changes and 27% of local pain. A comparison of side effects incidence between groups revealed that Group 3 (etilefrine 3 mg) reported significantly lower rates of haemodynamic changes ($p=0.001$), since no patient in this group reported blood pressure or heart rate increase, and significantly lower rates of local pain (10% of patients, $p<0.0001$). A logistic regression analysis predicting the risk of any side effects occurring after etilefrine administration showed that the only statistically significant factor involved was dosage, favouring etilefrine 3 mg as safer to administer compared to 10 mg ($p<0.0001$; OR 0.26; 0.15-0.44 95% CI).

Conclusion: The administration of etilefrine 3 mg represent a safer and effective prophylaxis of prolonged erection in patients who demonstrated a RI >1 and full penile rigidity during DPCDU.

INTRODUCTION

Dynamic Penile Colour Doppler Ultrasound (DPCDU) is currently regarded as a second-level diagnostic test in patients with Erectile Dysfunction (ED), of which vasculogenic aetiology is suspected. Usually, potential candidates for this exam are patients with diabetes mellitus, cardiovascular comorbidities, peripheral vasculopathy and poor responders to phosphodiesterase type 5 inhibitors (PDE5is) treatment [1]. Some authors have recently suggested that DPCDU may also be of use in planning treatment strategies with low-intensity shock wave (LI-SWT), since it provides important information about penile haemodynamics [2].

The operating procedure for performing a DPCDU exam may present a few variations among practitioners, despite the

presence of guidelines and recommendations on the subject, but the key steps and their sequence are mostly preserved. After the acquisition of the informed consent, the exam is performed in a quiet and reserved room. The penis is previously scanned in B-mode, then a single or a mixture of vasoactive agents is injected in the corpora cavernosa (IntraCavernosal Injection, ICI). It is reported that prostaglandin E1 is the most commonly used agent, followed by phentolamine and papaverine. Multiple evaluations of vascular parameters such as Peak Systolic Velocity (PSV) and Resistance Index (RI) are then performed and recorded. Audio-visual stimulation with or without manual genital self-stimulation may be considered for aiding the patient in achieving the highest degree of penile rigidity during the procedure. If a false-positive vascular dysfunction is suspected, for example in a patient suffering from anxiety or in the presence of other interfering factors that prevent the achievement of full rigidity, a re-dosing of the vasoactive agent may be considered [1,3].

Intracavernous injections of vasoactive agents are essential for DPCDU, allowing the operator to evaluate the penile vascular status. On the other hand, there are reports of prolonged erection and priapism in 1-10% occurring after DPCDU, depending on the type of the adopted pharmacological stimulation [4]. For this reason, various sympathomimetic drugs have been used to prevent this side effect. The alpha-agonist etilefrine, due to its short duration of action, is reported to prevent priapism and is suggested in patients who achieve a complete rigidity and a RI > 1, which represents a prognostic factor for prolonged erection after DPCDU [5]. However, etilefrine is contraindicated in patients with severe hypertension, congestive cardiac failure and heart arrhythmia due to potential haemodynamic effects. In order to reduce the risk of systemic haemodynamic adverse events while ensuring the prevention of priapism, we tested different dosages of etilefrine administered after DPCDU in a single center study.

MATERIALS AND METHODS

We performed a retrospective analysis on a prospectively collected database including 1599 patients treated with etilefrine to prevent priapism after undergoing DPCDU with PGE1.

The examination protocol at our center is the same for all patients: DPCDU is executed in a quiet room with the exclusive presence of a physician and a nurse. Antiaggregant and anticoagulant therapy is stopped seven days before the test and substituted with low molecular weight heparin to prevent possible bleeding in the site of injection and haematoma formation. At 3, 10 and 20 minutes after intracavernous injection of PGE1 at dosages of 20 mcg, the PSV and the RI is recorded at the cavernous arteries bilaterally at the peno-scrotal angle. PSV is considered normal when ≥ 35 cm/sec; border-line between 30 cm/sec and 35 cm/sec and pathologic if < 30 cm/sec. RI > 1 is considered in the range of normality, a value between 0.90 and 1 is classified as border-line while a result <0.90 is pathologic.

Once the second evaluation is completed, the patient is left alone for ten minutes and invited to perform a manual genital stimulation to achieve an erection. Before performing the third evaluation, the physician asks the patient to report if the result obtained is similar, better or worse than the erection observed in other circumstances. Contextually, the clinical response is classified at every measurement in five different grades (1= no tumescence, 2= mild tumescence, 3= tumescence without rigidity, 4= partial rigidity, 5= full rigidity).

In those patients in which a RI > 1 is observed in association with full rigidity, priapism prevention with etilefrine is administered. Following the administration of etilefrine, blood pressure, cardiac frequency and penile detumescence status are monitored at baseline, and then at 5, 15, 30 and 60 minutes and then the patients are dismissed. Regarding cardiovascular parameters, we decided to consider only a blood pressure increase of more than 20 mmHg and a cardiac frequency acceleration of more than 15 bpm, as clinically significant. Any lesser variation was deemed as clinically insignificant. This is because in literature there is still much debate on what exactly constitutes a "significant" blood pressure and/or cardiac frequency variation, due to a large intra-subject variability in general population [6,7].

Patients are then advised to report eventual adverse events occurred at home in the 7 days following the exam by means of a phone call: this is a very unusual occurrence that no patient in our sample population experienced. All these data are recorded in the patients' files for future reference. A full clinical history of those patients, with regards to andrological indication for the exam (Erectile Dysfunction, Peyronie's disease or both) and overall comorbidities (diabetes mellitus, hypertension, cardiovascular conditions, smoking habit, pelvic surgery history) as well as the result of DPCDU (RI), complement the patient file.

Due to concerns about etilefrine cardiovascular safety, the commonly used dosage adopted in our institution has been gradually lowered over the course of the last 10 years (2010-2019). Therefore, while reviewing the patients' files, we managed to collect clinical data on three distinct group of patients who received differing dosages of etilefrine. Group 1 included patients treated with etilefrine 10 mg after DPCDU with PGE1. Group 2 consisted of patients receiving a lower dose of etilefrine: 5 mg. Group 3 received an even lower dose of etilefrine: 3 mg. Of course, in our sample we only included patients with a RI > 1 in association with full rigidity, who therefore were administered etilefrine as priapism prevention after undergoing DPCDU.

All data was obtained from the patients' files. Privacy authorization for scientific use of personal data was obtained at the time of the file completion.

Statistical analysis

Baseline clinical characteristics and adverse events reported after etilefrine dosing were compared between the three groups and significant differences were tested with Kruskall-Wallis and Chi^2 test for continuous and categorical variables, respectively. The association between different etilefrine dosages and the risk of adverse events was then tested with a logistic regression model adjusted for clinically relevant factors.

RESULTS

Overall, 750 patients met the criteria of the study and were included in the analysis, with 150 receiving etilefrine 10 mg (Group 1), 300 receiving etilefrine 5 mg (Group 2) and 300 receiving etilefrine 3 mg (Group 3).

The three groups were found to be statistically comparable in terms of age, DPCDU findings (RI), indications for the exam, prevalence of diabetes and cardiovascular comorbidities. On the other hand, there were some differences in terms of other characteristics: Group 1 had the lowest rate of pelvic surgery history (4%) and the highest prevalence of anxiety (19%) and smoking history (43%) among its population. Group 2 had the highest rate of depression (55%) (Table 1).

All groups reported a 100% success rate of priapism prevention after administration of etilefrine, independently of the dosing (Table 1). Overall, side-effects were infrequent, mild and self-limiting: the highest incidence was in Group 1 with a 5.3% incidence of haemodynamic changes and 27% of local pain. A comparison of side effects incidence between groups revealed that Group 3 (lowest dosage of etilefrine at 3 mg) reported significantly lower rates of haemodynamic changes (p=0.001), since no patient in this group was affected, and significantly lower rates of local pain (p<0.0001) with only 10% of patients affected (Table 2).

A logistic regression analysis predicting the risk of any side effects occurring after etilefrine administration showed that the only statistically significant factor involved was dosage. In fact, etilefrine 5 mg yields a lower risk of side effects compared to 10 mg (p=0.03; OR 0.61; 0.39-0.95 95% CI), while etilefrine 3 mg yields the lowest risk possible when compared to 10 mg (p<0.0001; OR 0.26; 0.15-0.44 95% CI). Other demographic and clinical factors considered in this study appeared not to be relevant (Table 3).

DISCUSSION

We investigated the safety and efficacy of different dosages of etilefrine administered after DPCDU in patients at higher risk of priapism. Our data showed that even the lower dose of 3 mg was effective in preventing priapism while ensuring the lowest risk of overall side effects thus including haemodynamic alterations and local pain.

There have been literature reports of prolonged erection and priapism after vasoactive drug administration in the context of DPCDU ranging from 1 to 10% of patients [4,8,9]. This data, along with the well-known pathological consequences of priapism, in the form of smooth muscle degeneration and sinusoidal thrombosis possibly preceding permanent damage to penile tissues [10,11], lead to a justifiable caution by some practitioners when using vasoactive agents in DPCDU. A first attempt to adopt another vasoactive drug to stave off prolonged erections and priapism was done with epinephrine and norepinephrine, which were abandoned due to the onset of severe cardiovascular side effect. This prompted a search for other possible solutions [12,13].

Phenylephrine has been proposed for reversal of prostaglandin-induced erections after DPCDU with good results: as reported by Jiang et al., reversal of prolonged erections was achieved in all 44 patients involved, with minimal side-effects (mild blood pressure change, throbbing sensation in the penis). However, the population of this study only consisted of patients affected by Peyronie's Disease [14]. Etilefrine has been proposed as a treatment in a wide range of priapism conditions. For example, there are authors who advocate its use in stuttering priapism affecting patients with sickle cell disease, although larger analyses found a low level of evidence [15,16]. When administered intravenously, etilefrine can increase the pulse rate, cardiac output, and central venous pressure and mean arterial pressure of healthy individuals due to its effects both on β1 and α receptors [17]. Despite these known side-effects, there are reports in literature regarding its use as ICI for priapism prevention after DPCDU, although few, far between and often small in population size. Intracavernous injections of low dosages (1-2 mg) have been cautiously attempted in a very small Japanese case series (4 patients), in which the author also suggested repeated injections in case of persisting erection. The patients involved reported a prolonged erection after injection of papaverine 40 mg. Nevertheless, all 4 patients achieved complete detumescence after etilefrine single or repeated

Table 1: Baseline characteristics according to dosing groups.

	Group 1= 10 mg (N=150; 20%)	Group 2= 5 mg (N=300; 40%)	Group 3 = 3 mg (N=300; 40%)	p-value
Age (yrs)	50 (37, 59)	51 (40, 59)	51 (42, 58)	0.2
RI	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.1)	0.006
Indication for PDU N(%)				
ED	128 (85%)	232 (77%)	237 (79%)	0.3
PD	17 (11%)	54 (18%)	45 (15%)	
ED + PD	5 (3.3%)	14 (4.7%)	18 (6.0%)	
Diabetes N(%)	20 (13%)	51 (17%)	37 (12%)	0.2
CVD N(%)	12 (8.0%)	17 (5.7%)	26 (8.7%)	0.3
Hypertension N(%)	19 (13%)	49 (16%)	81 (27%)	0.0002
Pelvic surgery N(%)	6 (4.0%)	51 (17%)	19 (6.3%)	<0.0001
Anxiety N(%)	28 (19%)	40 (13%)	8 (2.7%)	<0.0001
Depression N(%)	80 (53%)	166 (55%)	62 (21%)	<0.0001
Smoking history N(%)	64 (43%)	95 (32%)	52 (17%)	<0.0001
Priapism Prevention N(%)	150 (100%)	300 (100%)	300 (100%)	

Abbreviations: CVD: Cardiovascular Disease; ED: Erectile Dysfunction; PD: Peyronie's Disease; PDU: Penile Doppler Ultrasound; RI=Resistance Index

Table 2: Side effects after different etilefrine dosing.

	Group 1= 10 mg (N=150; 20%)	Group 2= 5 mg (N=300; 40%)	Group 3 = 3 mg (N=300; 40%)	p-value
Haemodynamic changes N(%)	8 (5.3%)	7 (2.3%)	0 (0%)	0.001
Systolic pressure peak N(%)	5 (3.3%)	7 (2.3%)	0 (0%)	0.01
Heart rate increase N(%)	3 (2.0%)	0 (0%)	0 (0%)	0.002
Local pain N(%)	40 (27%)	57 (19%)	30 (10%)	<0.0001

Table 3: Logistic regression analysis predicting risk of side effects (any).

	OR	95% CI	p-value
Age	0.99	0.98, 1.01	0.4
RI	0.48	0.04, 5.25	0.5
Hyperthension	0.97	0.58, 1.64	0.9
CVD	1.17	0.57, 2.39	0.7
Anxiety	1.49	0.86, 2.58	0.2
Etilefrine dosage 10 vs. 5	0.61	0.39, 0.95	0.03
10 vs 3	0.26	0.15, 0.44	<0.0001

Abbreviation: CVD: Cardiovascular Disease; RI: Resistance Index

administration [18]. Higher dosages (etilefrine 10 mg) were used in a more recent, small-sized, case series including 8 patients with prolonged erection after a vasoactive drug injection and 15 patients who experienced involuntary and persistent erections during transurethral surgery. Detumescence was achieved in all patients, despite 2 cases of local haematomas and 1 patient requiring aspiration of cavernosal blood followed by a second administration of etilefrine 10 mg. It is important to note that even though the dosage of etilefrine was quite high, no systemic side-effects were observed [19]. More recently, etilefrine was included in a study about timely treatment of priapism induced by drugs for erectile dysfunction, along with local remedies (such as cooling measures or physical exercise), terbutaline and cavernosal drainage and flushing. These therapeutic solutions were intended as treatment and not as prevention for priapism, so they were administered only in 31 patients experiencing an actual priapism event, with erection time lasting upwards of 4 hours. 19 subjects received an intracavernosal dose of etilefrine of 10 mg or less, achieving detumescence with no particular systemic side-effects reported. There were 3 patients who reported a worsening in erectile function after treatment, but it is unsure whether this was due to the drugs used to treat the priapism event rather than the pathological sequelae of priapism itself [8]. Cormio et al., proposed the administration of etilefrine 5 mg in those patients who achieved a complete erection with a RI > 1 after ICI of PGE1: of 37 treated patients, none experienced adverse events. On the other hand, according to their experience, etilefrine administration was unnecessary in patients with a RI ≤ 1, because they consistently presented spontaneous detumescence within 2 hours after pharmaco-stimulation [5].

In the present study, we analyzed data from our database of patients who underwent DPCDU with administration of etilefrine as priapism prevention if RI proved >1 with full penile rigidity, as per our standard operating procedure. Over the last 10 years, we report that no patient out of the 750 who underwent etilefrine administration after DPCDU suffered prolonged erections or priapism, independently of the dosage. It is important to note that the effectiveness of etilefrine in preventing priapism remained optimal even with consecutively lower dosages, which in time we brought from 10 mg to 5 mg and ultimately to 3 mg, due to concerns about cardiovascular safety.

Regarding side effects, we can say that in our experience they have always been mild and self-resolving. Moreover, the incidence of undesired occurrences has always been fairly low, reaching a maximum of 5.3% in terms of haemodynamic changes and 27% in terms of local pain in Group 1 (etilefrine 10 mg). Even so, reducing the dosage to 5 mg and then to 3 mg has significantly decreased the incidence of any side effects, up to the point that Group 3 (etilefrine 3 mg) reported no cases of haemodynamic changes and few cases of local pain.

Based on the data provided, we can assume that an ICI of etilefrine at the lowest dosage of 3 mg can be an effective and safer method for preventing prolonged erections and priapism risk after a DCPDU with administration of vasoactive agents in patients who demonstrated a RI >1 with full penile rigidity during the exam.

In our opinion, one of the strengths of our study is the relevant sample size when comparing to the few specific studies on the subject. Moreover, its implications may have an immediate impact in clinical practice when defining what a standard operating procedure for DPCDU with vasoactive agent's administration should be. The limitations of this study mainly reside in its retrospective nature, which prevents us from further characterizing the sample population (e.g. by the demographical and clinical point of view) and from having a control group to compare to.

CONCLUSION

According to our experience, a low dose of etilefrine

administered at 3 mg after DPDCU represents a safer and effective prophylaxis for prolonged erection and priapism in patients who demonstrated a RI >1 and full penile rigidity during the exam.

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Cite this article

Penile Dynamic Colour Doppler Ultrasonography: A Retrospective Study on 750 Prospectively Collected Patients. JSM Sexual Med 4(6): 1048.