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**Prostate Cancer: Hormonal Treatment and Treatment of
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Intracavernous Calcitonin Gene-Related Peptide Plus Prostaglandin E₁: Possible Alternative to Penile Implants in Selected Patients

Key Words

Impotence
Venous ligation
Smooth muscle physiology
Corpus cavernosum
Electromyography
Calcitonin gene-related peptide
Pharmacotherapy

Abstract

The implantation of a penile prosthesis is still the ultima ratio for patients with erectile dysfunction who fail other treatment options such as pharmacotherapy and penile venous surgery. Despite mostly favorable results regarding restoration of erectile capacity, penile allografts are often not accepted for various reasons. Therefore, pharmacotesting with a mixture of calcitonin gene-related peptide and prostaglandin E₁ (CGRP/PGE₁) was offered to different selected patients populations: 28 patients with erectile dysfunction and venous leakage who failed penile venous surgery, 28 patients with erectile dysfunction and venous leakage (who refused penile venous surgery) and 12 patients without venous leakage, but poor response to maximum doses of papaverine/phentolamine, received 5 µg CGRP plus 10 µg PGE₁. Erections sufficient for intercourse were noted in 19/28 (67.9%), 20/28 (71.4%) and 11/12 (91.7%) patients, respectively. Our data show that a combination of CGRP and PGE₁ may be an alternative to penile implants in selected patients.

Introduction

Cavernous smooth muscle tissue plays a major role in the induction and maintenance of a normal erection [1, 2]. In addition to adequate arterial inflow, relaxation of the cavernous smooth muscle is required, resulting in a strong reduction of venous outflow. Theoretically, insufficient venous outflow reduction can be caused by ectopic veins, incomplete cavernous relaxation or pathologic alterations of the tunica albuginea [3–5]. Standardized intracavernous pharmacotesting has been shown to be of high predictive value for the diagnosis of venous leakage

[6]. However, in some patients not responding to repetitive maximum doses of conventional pharmacotherapy, no venous leakage is found by cavernosometry and cavernosography. In these patients the etiology of impotence remains obscure and cannot be assessed by current diagnostic tests when arterial disease has been ruled out.

In patients with venous leakage, penile venous surgery is a common treatment option. However, despite increasing knowledge about the pathomechanism of venoocclusive dysfunction, the results of venous ligation procedures often remain dissatisfying. The ultima ratio for patients who fail penile venous surgery and who do not respond to

conventional pharmacotherapy is still the implantation of a penile prosthesis.

This study was undertaken to identify therapeutic alternatives for patients who failed penile venous surgery, who do not respond to conventional pharmacotherapy or who refuse penile allografts for various reasons.

Patients and Methods

The routine workup of patients with erectile dysfunction in our impotence clinic consists of a detailed case history including a questionnaire, a sexual case history by a psychiatrist where indicated, a complete physical examination, routine blood laboratory, corpus cavernosum electromyography [7], pharmacotesting with a mixture of papaverine and phentolamine and Doppler ultrasonography. Where indicated, pharmacocavernosometry/-graphy and digital subtraction angiography are done.

Pharmacotesting was done in a relaxed atmosphere after informed consent had been obtained. Increasing doses of a mixture of papaverine (15 mg/ml) and phentolamine (0.5 mg/ml) were given, starting with a dose of 0.2 ml. Only 1 injection per day was given to avoid prolonged erections. The dose was increased to a maximum of 2.0 ml depending on the erectile response. Erections were evaluated by a urologist by inspection and palpation and graded as follows: E 0 = no response; E 1 = slight tumescence; E 2 = medium tumescence; E 3 = full tumescence; E 4 = full tumescence with medium rigidity sufficient for intercourse, E 5 = full erection. If 2 ml of the mixture failed to induce an erection sufficient for intercourse despite additional manual self-stimulation, venous leakage was suspected and the patient was offered pharmacocavernosometry/-graphy for evaluation of the venoocclusive system.

For corpus cavernosum electromyography (the term SPACE – single potential analysis of cavernous electrical activity – was abandoned in favor of the more precise and neutral term CC-EMG – corpus cavernosum electromyography – by the consensus committee at the First International Workshop on Smooth Muscle EMG Recordings/Leimyogram in Mannheim (FRG) [8] 2 coaxial needle electrodes (Dantec 9013 L) were inserted bilaterally into the cavernous bodies and advanced until the tips of the electrodes were located centrally. The signals were processed by different electrophysiological units (WIEST SPACE, Dantec Neuromatic 2000), displayed continuously on a monitor screen (Dantec 2000) and simultaneously recorded (WIEST SPACE). Interpretation of the recordings was done according to previously published data [7]. Since 9/92 EMG signals were recorded on-line with a personal computer and data were processed using an especially designed software on the basis of the Fast-Fourier analysis [9].

Doppler ultrasonography of the penile arteries was performed as described elsewhere [10]. For pharmacocavernosometry/-graphy the left corpus cavernosum was punctured with a 19-gauge needle under sterile conditions and connected to a perfusion pump. The right corpus cavernosum was punctured with a 26-gauge needle and connected to a transducer for pressure recording (WIEST Cavopump, Wiest, Germany). To induce cavernous smooth muscle relaxation, 30 mg of papaverine and 1 mg of phentolamine were injected intracavernously via the left cannula. After 10 min and subsequent to cavernous relaxation, cavernosometry was performed by perfusing the

penis with warm (37°C) saline with a flow rate of 150 ml/min. As soon as rigidity was reached, the minimum flow to maintain a full erection was determined ('maintenance flow'). After infusion of undiluted nonionic contrast medium, X-ray films were taken in anteroposterior and oblique (30°) positions. After opacification, the penis was perfused with normal saline to wash out the contrast medium. The needles were removed and the puncture sites were compressed manually. Flow rates exceeding 14 ml/min were considered abnormal [11–13].

All 129 patients with documented venous leakage were offered penile venous surgery and counseled about alternative therapeutic options.

Penile venous surgery was done as follows: A midline incision was done over the dorsum of the penis, then the superficial dorsal veins were ligated and the deep dorsal veins were resected from about 1 cm proximal to the suspensory ligament to the distal 1/3 of the penile shaft.

Since previous studies showed a higher response rate of a combination of calcitonin gene-related peptide (CGRP) plus prostaglandin E₁ (PGE₁) as compared to PGE₁ alone [14], we offered this combination (5 µg CGRP plus 10 µg PGE₁) to patients with venous leakage who failed penile venous surgery, to patients with venous leakage who refused penile venous surgery and to patients without documented venous leakage who failed pharmacotherapy with papaverine/phentolamine. Prior to the injections all patients were extensively informed about the experimental character of this drug combination as well as possible side effects. The study protocol was approved by the Ethics Committee of the Medizinische Hochschule Hannover.

Results

After a comprehensive workup including pharmacotesting, venous leakage was suspected in 160/448 patients (35.7%). Insufficiency of the venoocclusive system was diagnosed in 129/160 (80.6%) or 129/448 (28.8%) patients, respectively. As therapeutic options penile venous surgery, implantation of a penile prosthesis, the use of a vacuum constriction device or a trial with CGRP/PGE₁ injections were offered. After extensive counselling, 84 patients underwent penile venous surgery, 28 patients opted for a trial with CGRP/PGE₁, 5 patients (all with concomitant Peyronie's disease) underwent implantation of a penile prosthesis and 2 patients with dysplastic arterial disease underwent arterial revascularization and penile venous surgery. The use of a vacuum constriction device was favored by 5 patients. The remaining 5 patients are either awaiting or refused further therapy (table 1).

In 31/160 patients (19.4%) without adequate response to 30 mg papaverine plus 1 mg phentolamine, venous leakage could not be documented by cavernosometry and -graphy. 28 patients who failed penile venous surgery underwent pharmacotesting with 5 µg CGRP plus 10 µg PGE₁. Of these, 19 (67.9%) achieved erections sufficient

Table 1. First-line management in 129 patients with erectile dysfunction and venous leakage

Penile venous surgery	84
CGRP/PGE ₁ trial	28
Implantation of penile prosthesis	5
Vacuum constriction device	5
Arterial reconstruction (Hauri) and penile venous surgery	2
Awaiting therapy or refused treatment	5

Values are number of patients.

for intercourse. In addition, 28 patients with venous leakage who refused penile venous surgery and 12 nonresponders to papaverine/phentolamine (but without venous leakage) opted for pharmacotesting with CGRP/PGE₁. 20/28 (71.4%) and 11/12 (91.7%) patients had E 4 or E 5 responses. In the latter highly selected population the etiology of erectile dysfunction remained unclear despite a thorough diagnostic workup (significant arterial disease had been ruled out by Doppler ultrasonography).

The patients who responded to pharmacotherapy with CGRP/PGE₁ entered another study to evaluate the safety and efficacy of CGRP/PGE₁ autoinjection therapy. Up to now no significant side effects have been reported in this group after up to 80 and more autoinjections per patient [14]. Only 2/40 patients (5.0%) reported significant intrapenile pain associated with the injection.

A total of 13 patients (after failed penile venous surgery and/or failed CGRP/PGE₁ pharmacotesting) underwent implantation of penile allografts and 10 patients opted for a vacuum constriction device. The remaining patients refused further treatment.

Discussion

The management of erectile dysfunction associated with or due to venous leakage is far from being standardized despite better diagnostic tests to evaluate the etiology of impotence. As demonstrated in previous studies [6], standardized pharmacotesting with vasoactive substances was shown to have a high predictive value for the evaluation of the venoocclusive system. Although short-term results of the presumably causative therapy, penile venous surgery, often seemed to be promising [15], the outcome with longer follow-up tends to be disappointing [16]. Concomitant arterial disease was claimed to be one of the predisposing factors for the failure of venous sur-

gery and, therefore, reconstructive vascular surgery was promoted with various intermediate and long-term results [17, 18]. Incomplete cavernous relaxation due to autonomic dysfunction or myogenic cavernous degeneration may be one of the possible etiologies of the insufficiency of the venoocclusive system [19]. Since CC-EMG was shown to be a minimally invasive and reproducible method for the evaluation of autonomic cavernous innervation and cavernous smooth muscle integrity [7], we evaluated our patient population after penile venous surgery in retrospect. Of the 38 patients who failed penile venous surgery, 30 (78.9%) had abnormal CC-EMG patterns, whereas 30/39 patients (76.9%) who had sufficient erections with or without additional intracavernous injections, had normal CC-EMG patterns. This difference was statistically highly significant ($p < 0.001$, χ^2 test) [own unpubl. data]. Thus, routine CC-EMG evaluation in patients with erectile dysfunction and venous leakage contributes significant predictive information and may alter the decision making in this patient population.

The ultima ratio after failed venous surgery and conventional pharmacotherapy remains the implantation of a penile prosthesis. However, despite mostly favorable results, many patients reject allografts for various reasons. In our experience, many patients also do not accept vacuum constriction devices due to their cumbersome handling. Since the classical drugs for autoinjection therapy (papaverine, papaverine plus phentolamine, PGE₁) induce a full erection in only 50–70% of an unselected population [20–25], newer, more potent substances or mixtures with a higher response rate are needed [26]. CGRP, along with other substances, was shown to play a possible role in the regulation of the smooth muscle tone [27]. Preliminary data show that a combination of CGRP and PGE₁ has a higher response rate than PGE₁ alone, with less side effects, such as intrapenile pain [28]. The pain reducing effect of CGRP/PGE₁ may be due to the anti-inflammatory effect of CGRP [29] and the reduced dose of PGE₁. We therefore offered, after extensive counseling about possible risks and side effects and after informed consent had been obtained, this combination to patients after failed penile venous surgery or as an alternative to penile venous surgery. In addition, patients without venous leakage as documented by cavernosometry and cavernosography but insufficient response to maximum doses of papaverine/phentolamine (despite the absence of significant arterial disease) were offered this drug combination. In these highly selected patient populations drugs with a higher erectile potential than papaverine/phentolamine or PGE₁ are needed. Pharmacotesting with CGRP/

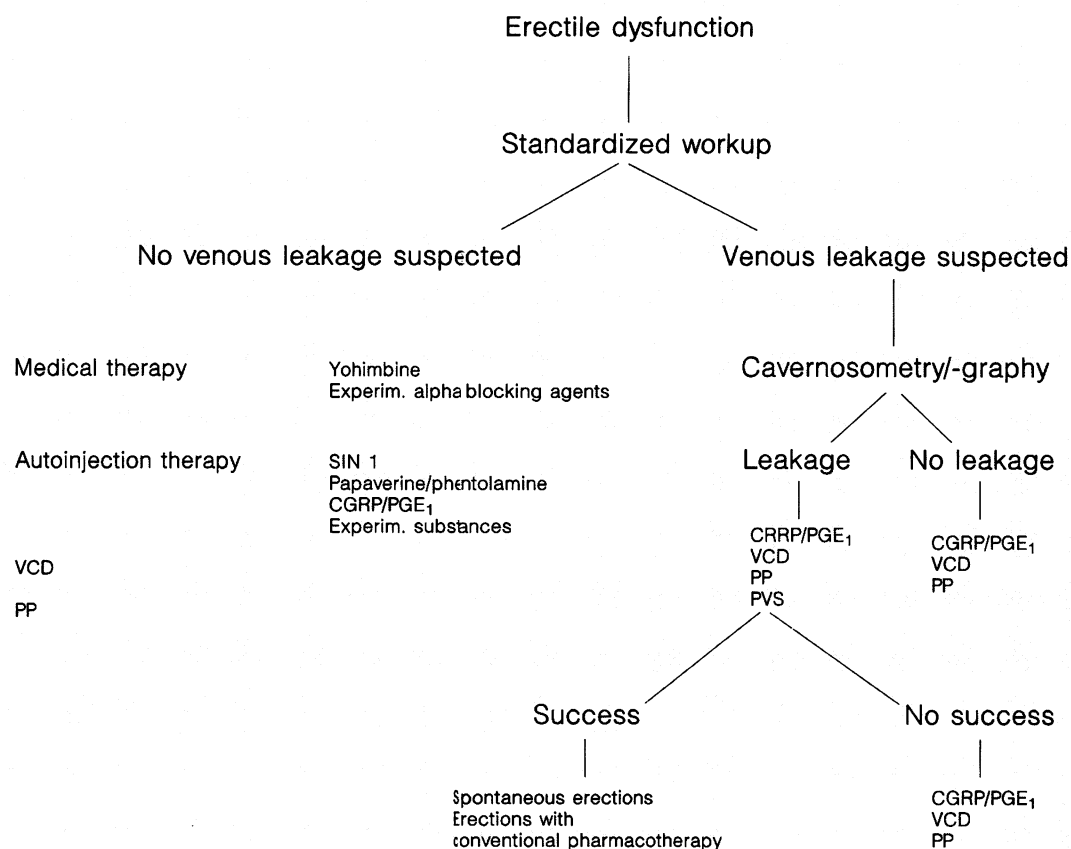


Fig. 1. Erectile dysfunction – current management at Medizinische Hochschule Hannover. VCD = Vacuum constriction device; PP = penile prosthesis; PVS = penile venous surgery.

PGE₁ induced sufficient erections in 67.9, 71.4 and 91.7% of patients, respectively.

The higher response rate of CGRP/PGE₁ compared to papaverine, papaverine/phentolamine or prostaglandin alone may be explained by the different and potentially additive effector mechanisms of CGRP and PGE₁. CGRP relaxes smooth muscle cells by hyperpolarization via potassium channel opening and cyclic adenosine monophosphate stimulation [30, 31]. PGE₁ acts through specific receptors on the smooth muscle cell surface.

In an ongoing study, the long-term efficacy and safety of this drug combination was evaluated with promising results; so far, no significant complications such as prolonged erections or fibrosis were noted after up to 80 and more injections per patient [14]. We therefore think that CGRP/PGE₁ may be a valuable alternative to penile implants as well as vacuum constriction devices in select-

ed patients. However, it should be stressed that the experimental and clinical experience with this drug combination is still relatively limited. Despite favorable data, the use of CGRP/PGE₁ should currently be restricted to selected patients in well controlled clinical studies. For example, no data are yet available regarding the possible risk of prolonged erections in patients also responding to less potent substances like papaverine or prostaglandin alone. In addition, toxicological data for CGRP are restricted to the rabbit model, where human CGRP caused signs of slight to moderate inflammation [own unpubl. data]. Taken this together, the use of intracavernous CGRP/PGE₁ in patients with impotence should still be regarded as experimental and patients should be made aware of the experimental character of this treatment option.

The therapy of erectile dysfunction is nowadays too complex that it possibly could be a one-strategy or even a one-drug therapy. The increasing complexity of the etiologies and diagnostic modalities of erectile dysfunction requires the availability of drugs with different effector mechanisms and different erectile potentials. Currently, we recommend different substances to different patient populations: For a standardized dose response we use a mixture of papaverine and phentolamine. In case a patient responds very well or with a prolonged erection to small doses of this combination (<0.7 ml), we offer the nitric oxide donor linsidomin chorhydrate (SIN 1) [32]. The efficacy of this substance has been shown to be excellent in this patient population and no prolonged erections have been observed so far in more than 100 patients. In contrast, in patients who needed higher doses of papaverine/phentolamine (>0.7 ml) for the induction of an erection, the efficacy was significantly lower. These data demonstrate that SIN 1 is less potent but safer than papaverine/phentolamine [33]. Therefore, patients who respond well to moderate to maximum amounts of papaverine/phentolamine (0.8–2.0 ml) are maintained on this combination.

All other patients are offered cavernosometry and cavernosography and counseled about the possible alternatives: penile venous surgery, use of a vacuum constriction device, implantation of a penile prosthesis and autoinjec-

tion therapy with CGRP/PGE₁ (fig. 1). As stated before, CGRP/PGE₁ should currently not be regarded as a first-line treatment for an unselected patient population but should be considered for patients who need a more potent smooth muscle relaxing substance.

The finding 'venous leakage' may be a symptom of multifactorial etiology consisting of arterial, autonomic, myogenic, and venogenic pathology. Thus, evaluation of the autonomic cavernous innervation and smooth muscle intactness by CC-EMG provides additional predictive information in regard to the outcome of venous surgery. Based on the data of this study, we now routinely counsel our patients with erectile dysfunction and venous leakage and offer alternatives to penile venous surgery, such as pharmacotherapy with CGRP/PGE₁, use of a vacuum constriction device and implantation of a penile prosthesis.

In conclusion, our data show that success of penile venous surgery depends on proper patient selection; routine CC-EMG contributes significant predictive information in patients with erectile dysfunction and venous leakage. The combination of CGRP and PGE₁, as well as other possible substances or combinations of substances, may prove to be a valuable option in highly selected patients. Due to the experimental nature of new drug regimen, patients should be followed closely.

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