

Original Article

Intracavernous Injection of Prostaglandin E1 for the Treatment of Erectile Dysfunction in Spinal Cord Injured Patients: Experience with 30 Patients

Musaed Faraj Khamees, Maria Kondeva Ivanova, Mohammed Akbar Ali, Tiberiu Raibulet
Physical Medicine and Rehabilitation Hospital, Sulaibikhat, Kuwait

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ABSTRACT

Objectives: To evaluate the efficacy of intracavernous injections of alprostadyl (Caverject) in the treatment of erectile dysfunction in patients with spinal cord injury (SCI) and to determine the mean necessary dose to obtain functional erection.

Material and Methods: Thirty patients aged between 20 to 44 years, duration of lesion from one to 13 years and level of SCI from C₅ incomplete to L₃ complete, were included in the study. The treatment started with a minimal dose of 1.125 micrograms and the dosage was titrated to achieve rigid erection. Following the establishment of the effective dose, the patients were trained in the technique of self-injection. They returned periodically for follow up.

Results: Twenty seven patients achieved functional erection (Schramek grade 4 or 5) with a dose equal or less than 20 micrograms (mcg) of Caverject. The average effective dose was 11.75 ± 4.6 mcg. Average duration of erection was 48.3 minutes. No side effects from the treatment were observed except discomfort in two patients and mild penile pain in one patient. 76% of the patients were satisfied and very satisfied with the treatment.

Conclusion: Intracavernous injections of Caverject are effective and safe therapy for erectile dysfunction provided that individual dose is established by titration, the patients are trained in the technique of self-injection

KEYWORDS: alprostadyl, erectile dysfunction, spinal cord injury

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent inability to obtain or maintain an erection for satisfactory sexual relations^[1,2]. The last decade has witnessed major advances in the understanding of erection and its underlying mechanisms. A complex hemodynamic process is being delineated, involving four basic elements, namely, sinusoidal relaxation, arterial inflow, venous occlusion and neural control^[3,4]. Both sympathetic (lower thoracic level) and parasympathetic (sacral level) nerves take part in this control. In spinal cord injury (SCI), sacral medulla remains intact in the vast majority of the patients and erection can usually be achieved by local stimulation of the genital region, by bladder filling or by spasms. Psychogenic erections may be normal in patients with lumbar lesions, leaving connections with lower thoracic levels intact. About 80% of men with SCI will experience some erectile ability. The overwhelming problem is the duration of the erection: tumescence and rigidity tend to fade away rather quickly making intercourse impossible^[5]. In the last 15 years, basic scientific research on ED has focused mainly on mechanisms of nitric oxide - mediated relaxation of the penile cavernous smooth muscle as a part of the

complex neurovascular event of erection^[6]. In SCI, the ineffective release of the penile neurotransmitter, nitric oxide, from nonadrenergic - noncholinergic nerves, prevents the initiation of erection^[7].

In the early 1980's Virag and Brindley were the first to report on clinical efficacy of intracavernosal injections of pharmacological agents to induce penile erection^[8,9]. Since that time, intracavernosal therapy with vasoactive agents has emerged as an important therapeutic option for male organic ED^[10-12]. Physiologic mechanisms that relax penile smooth muscle and elicit erection are mimicked by vasoactive drugs administered intra-cavernosally. Direct injection of the drug into the corpora cavernosa in SCI patients bypasses the initial psychoneurological stimuli necessary to initiate penile erection and directly causes corpora cavernosa smooth muscle relaxation by activating specific receptors and second messenger systems at the peripheral level^[13].

Treatment of ED in men with SCI has moved to minimally invasive therapies not involving surgery or devices. Intracavernosal therapy has been used effectively to induce erections in patients with SCI for more than a decade^[14-17]. Small dose of these medications are often adequate to induce rigid

Address correspondence to:

Dr. Maria Kondeva Ivanova, P.O.Box 31282, 90803 Sulaibikhat, Kuwait. Tel: 4889441, E- mail: ivanovi63@hotmail.com

erection in men with SCI because most of these men are young, have an intact arterial supply to the penis and a normal veno-occlusive mechanism. Other treatment options for restoration of erectile dysfunction in this group include, penile prosthesis insertion (that carries a significant risk of infection and erosion) and vacuum constriction device therapy (that is successful but believed by many to be cumbersome)^[18-20].

Prostaglandins have a role in the mechanism of natural erection^[21]. Alprostadyl is the synthetic form of prostaglandin E1, the natural prostanoid synthesized from di-homo-g-linoleic acid, a membrane phospholipid. Through activation of multiple regulatory mechanisms for the homeostasis of intracellular calcium, either directly by cyclic AMP or by cyclic AMP - dependent protein kinase, there is a decrease in its concentration that favors relaxation of smooth muscles^[22]. In addition to this direct action on the cavernous smooth muscle, prostaglandin E₁ reduces the adrenergic constrictor tone by inhibiting the release of noradrenaline through prejunctional receptors in adrenergic nerve endings^[23].

Intracavernous PGE1 (Caverject) was the first intracavernosal drug to obtain Food and Drug Administration (FDA) approval. PGE1 along with papaverine and phentolamine mesylate are the most common vasoactive drugs used for treatment of organic erectile dysfunction^[24-32].

To our knowledge, no study has been done so far in Kuwait for the effectiveness of intracavernous injection of Alprostadyl in men with SCI. The aim of this study was to find the effective dose, and the efficacy and safety of Alprostadyl (Caverject) for intracavernosal injection.

MATERIAL AND METHODS

Thirty men with SCI of at least one year duration, suffering from erectile dysfunction, were included in the study. Enrolment in the study was during or after completion of comprehensive rehabilitation program on inpatient and outpatient basis at the Physical Medicine and Rehabilitation Hospital, Kuwait. Potential limitations and adverse effects of treatment were extensively explained to the patients and they were asked to read and sign a formal consent for participation. Patients with hemoglobinopathy, bleeding disorders, Peyronie's disease, history of priapism and psychiatric diseases were excluded from the study. In addition, patients with poor visual acuity, morbid obesity and unstable cardiovascular disease were considered unsuitable candidates for treatment.

Patients were enlisted in the study after full sexual history was taken and neurological

evaluation, routine blood and urine analysis, culture/sensitivity test of urine were performed. The level and type of SCI were determined using ASIA classification. Current urinary tract infection was treated by antibiotics prior to injection.

The first stage of the program consisted of the dose titration of Caverject. Patients were instructed to void and remove condom if necessary. Alprostadyl (Caverject, Upjohn S.A Puurs, Belgium), is supplied as a sterile, freeze dried power in a 5 ml vial. After it was reconstituted with one milliliter of bacteriostatic water, each vial contained 20 µgms of Alprostadyl, 173 mg per milliliter of lactose and 47 µgms per milliliter of sodium citrate.

The penis was pulled away from the body until the skin was taut. A syringe with 27 to 30-gauge 1/2 inch needle was held at the right angle to the penis and the injection was given at the base of the penis on either side alternatively, avoiding visible veins. Pressure was applied to the injection site for five minutes or until bleeding stopped.

The first injection was delivered with a small amount of the drug (starting dose- 1.125 µgm). The physiatrist who gave the injection palpated the penis and rated rigidity as absent, partial or full at specified times after injection using Schramek grading system (Table 1)^[33]. A grade 4 or 5 erection was considered functional. Prolonged erection was defined clinically as an erection lasting from four to six hours and priapism as an erection lasting more than six hours.

A titration schedule was followed (second dose of 2.5 µgm and incremental doses of 2.5 µgm) until optimal dose was achieved. The optimal dose was one that produced erection suitable for intercourse and not exceeding a duration of 60 minutes.

The second phase started after proper instructions and training in the self-injection technique with the optimal dose established in the clinic. Patients were instructed to limit the use of injections to two injections per week with no more than one injection in any 24-hour period. They were also taught to inject right and left cavernosal body alternatively. Patients were warned to contact the clinic urgently if an erection persisted for more than three hours.

All patients were requested to return periodically to the clinic. At each follow up, the injection frequency, duration and consistency of erections were recorded. Patient's satisfaction from intracavernosal injections therapy with Caverject was rated in four grades - very satisfied, satisfied, not satisfied, and very unsatisfied with the treatment. The penis was carefully examined for

Table 1

Schramek's grading system

Schramek's grading system

Grade 1.	No erection
Grade 2.	Slight tumescence
Grade 3.	Full volume without rigidity
Grade 4.	Sufficient for sexual intercourse
Grade 5.	Full erection

nodules, haematomas or areas of induration. If necessary the dose of Caverject was adjusted by the treating psychiatrist.

RESULTS

Thirty patients (Six quadriparetic and 24 patients with paraplegia or paraparesis) with SCI of traumatic origin, aged between 20 to 44 years (mean age 27.3 years) were included in the study. The majority of patients were young, healthy men. Twenty three patients (76%) were aged 30 years and below. Eleven patients were married, 18 were single and one patient was divorced. All participants were having normal sexual activities prior to the accident. None of them had received intracavernosal injections prior to their enrollment in this study.

Twenty-seven (90%) patients sustained SCI in motor vehicle accidents, two had gun shot injury and one patient fell from a height and injured his spine. The average duration of SCI was nine years and two months (range 1-13 years). The level of SCI was from C5 to L3 according to ASIA classification.

Seventeen (56.7%) patients sustained complete whereas 13 patients had incomplete SCI.

Following intracavernosal injections of Caverject, sufficient erection for coital penetration was achieved in 27 patients (90%). Three patients (10%) responded with grade 3 penile tumescence.

The dose of Caverject required for functional erection was as follows: 2.5 µgm in two patients, five µgm in three patients, 7.5 µgm in three patients, 10 µgm in four patients, 12.5 µgm in six patients, 15 µgm in four patients and 20 µgm in five patients. The average dose necessary to obtain a grade 4 or 5 erection was 11.75 µgm of Caverject. Erection sufficient for coitus was achieved within 2 to 15 minutes (average 5.1 minutes) and lasted for 10 minutes to four hours. The average duration of erection was 48.3 minutes. Neither prolonged erections nor priapism were observed.

Two patients had discomfort and only one patient had mild pain following the intracavernous injection with Caverject. There have been no instances of systemic drug related reactions such as hypotonia, autonomic dysreflexia or cavernous fibrosis. Twenty-five patients (83.3%) used the effective dose established in the outpatient clinic as

maintenance dose for self-injections whereas two patients required an increase in the dose by 2.5 µgm.

Follow up at one year revealed discontinuation of treatment by five patients (attrition rate 17%).

The most important clinical end point, which was satisfaction with sexual activity, was reported by 76% of the patients.

DISCUSSION

In the current study we found a high success rate (90%) for intracavernosal injection therapy with Caverject and our results confirm, as do other reports in the literature, the efficacy of PGE1 in the treatment of erectile dysfunction^[8,27,34,35]. The efficacy of the vasoactive drugs in producing adequate erection is approximately 35% with papaverine alone, 69% for papaverine with phentolamine, 71% for PGE1 alone and 92% for the mixture of all three drugs^[11]. Tang *et al*^[30] evaluated the use of intracavernosal injection of PGE1 in a cohort of 15 men with SCI and found that 93.3% achieved Schramek grade 5 erection with an average duration of 59 minutes.

The response to PGE1 varies with the doses administered^[37]. In one study most of the responders to PGE1 (80%) attained maximal erection at dosages up to 20 µgm^[38]. Sheng *et al* evaluated 80 patients with different psychogenic and organic cause of impotence by intracavernous injection of 20 µgm PGE1 as an initial test dose^[39]. They reported a positive response in 63 (78.8%) patients. The average time for onset of response was 8.9 ± 5.0 minutes while the average time for maintenance of erection was 68.6 ± 3.3 minutes.

Linnet *et al*^[24] reported in a dose dependant study that all doses of alprostadyl were superior to placebo with significant dose response relation ($p < 0.001$), resulting in a higher response rate with increasing doses of the drug (from 2.5 µgm to 20 µgm). In our study, the erectile response was dose-dependent and even relatively low doses (equal or less than 20 µgm) were effective. Similar results have been reported in other studies^[40,41].

The main side effects of intracavernosal therapy with different formulations of alprostadyl are penile pain, prolonged erections, priapism and penile fibrosis^[42-44]. Penile pain is probably induced by alprostadyl itself since prostaglandins of the E group have a pain-sensitization action^[45].

Penile fibrosis may occur without intracavernosal therapy. It appears to be more common in men with erectile failure^[46] and has been reported after injections of other vasoactive drugs^[47]. Repeated needle injury and chronic microtrauma induced by sexual activity, especially in partly erect penis, may be contributing factors. Proper training of men in the injection technique

may minimize the risk of this complication. In this study, side effects were minimal and may be due to the low doses used and the careful titration for the effective dose.

In an attempt to reduce and avoid complications, other methods of delivery of alprostadyl have been sought. However, intraurethral application of PGE1 proved to be less effective for erectile dysfunction^[48,49]. Topical therapy has at this time only limited efficacy, indicating lower penetration of PGE1 through the skin and tunica albuginea^[50]. A combination of PGE1 plus procaine has also been studied as a potential alternative to reduce pain and discomfort after PGE1 application^[51].

New drugs, such as inhibitors of phosphodiesterase-5 that affect the breakdown of cyclic guanosine monophosphate look very promising. They are thought to work by enhancing nitric oxide mediated relaxation of corpus cavernosal smooth muscle. Existing evidence suggests that oral Sildenafil (Viagra) is a very highly effective and well tolerated treatment for erectile dysfunction associated with SCI^[52-55]. The dopaminergic agonist apomorphine, showed overall low rates of reference and will have limited applicability in patients with SCI^[56]. There is growing evidence that oral drugs will be dominant in the future management of sexual dysfunction and first line of treatment, while intracavernosal and intraurethral treatments are considered second line therapy and are usually indicated for patients who fail to respond to first-line therapy or for those who cannot use the least invasive forms of pharmacotherapy.

CONCLUSION

Intracavernosal alprostadyl is an effective and safe therapy for men with erectile dysfunction following SCI, provided that the dose is individualized by titration and the men are trained in the injection technique and supervised periodically during self injection. Results of this treatment in SCI appear to be quite good in the short term. Long-term evaluation of this treatment option in SCI is warranted.

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