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Comparative Evaluation of an Alternative Treatment for Erectile Dysfunction

Ochilov Shohsuvor Zokirovich
Mamayusupov Marat Qahramonovich
Pirnazarov Sardor Panjiyevich
Tuychiyev Sardor Azamatovich
e-mail: tuychiyev_9292@gmail.ru

Annation: Erectile dysfunction (ED) in men is defined as the persistent inability to achieve and maintain an erection sufficient for successful intercourse. [9] Although ED is a mild disorder, it is associated with mental and psychosocial health and significantly affects both the patient and his partner and family. ED affects 10-25% of middle-aged and elderly men. The demographic features of modernity, the emergence and popularization of new methods of treatment, a more tolerant attitude of patients and society towards the problem of ED have led to the fact that today it is detected more often, and healthcare costs are growing accordingly. Erectile dysfunction causes serious damage to the emotional and mental well-being of men, but many of them are hesitant to share their problem with others, and this should be dealt with by a doctor. The Massachusetts Study of Male Aging (2011) showed that 52% of men aged 40-70 years have a sexual dysfunction: 10% of respondents complained of complete erectile dysfunction, 25% of moderate and 17% of mild erectile dysfunction. [9]

Key words: urinary tract, pyelocaliceal system, premature ejaculation, erectile dysfunction, urinary tract infection.

Despite the fact that today there are many drugs in the treatment of erectile dysfunction,scientists don't stop developing new alternative drugs in this disease.

Thus, there is a need to develop an individual approach to the treatment regimen for each patient with erectile dysfunction, but such a tactic that would minimize the dose of drugs while maintaining the effect of their impact, which is of great socio-economic importance.

Vacuum generating devices provide passive stretching of the corpora cavernosa in combination with a compression ring located at the root of the penis to retain blood inside the corpora cavernosa. Thus, an erection caused by this method is not normal, since it does not use the pathways (nerve) of physiological erection. Efficiency (an erection sufficient for intercourse) is 90%, regardless of the cause of ED, and success ranges from 27-94%. Men with an interested, motivated and understanding partner note a high percentage of effectiveness. Long-term use of vacuum devices reduces the efficiency to 50-64% after 2 years. Most men who stop using the device do so within 3 months of starting [6].

The main adverse events include: pain, inability to ejaculate, petechiae, blueness and numbness (at least 30% of patients). A serious adverse event is skin necrosis. Therefore, you should avoid wearing the ring for more than 30 minutes. Vacuum devices are contraindicated in patients with impaired blood coagulation or receiving anticoagulants [63,64].

Vacuum devices are generally not perceived by young patients. However, they may be the method of choice in well-informed older patients who have infrequent intercourse.

Patients not responding to oral therapy can be treated with intracavernous injections with a high success rate (85%) [6]. The treatment of ED by administering vasoactive drugs was started over 20 years ago. Alprostadil (Caverject, Edex/Viridal) is the first and only drug recommended for the intracavernous treatment of ED. It is an effective monotherapy at a dose of 5-40mcg [7]. An erection occurs after 5-15 minutes and continues depending on the dose administered. The patient should learn self-injection during training programs (one or two visits). In cases of limited skills (inability), injections can be taught to a partner. (Fig-1.4) The use of special automatic pens avoids the appearance of the inserted needle and can simplify the technique.

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In the general ED population, the success rate of intracavernous alprostadil is over 70%, as is the case in subgroups of patients (eg, those with diabetes mellitus or cardiovascular disease). At the same time, sexual activity occurs in 94% of patients after injection and 87-93.5% of patients report successful intercourse.

Complications of intraquernosal alprostadil are: pain (50% of patients, after injection 11%), prolonged erection (5%), priapism (1%) and fibrosis (2%) [6]. Pain is reduced with prolonged use. It is alleviated by the addition of sodium bicarbonate or by the application of local anesthesia. With fibrosis, it is necessary to postpone the treatment program for several months. Systemic side effects are rare. Basically it is a slight hypertension when using large doses.

Contraindications are: a history of hypertension for the administration of alprostadil, patients at risk of developing priapism and patients with a bleeding disorder.

Despite these favorable indicators, intracavernous pharmacotherapy has a high dropout rate and limited patient compliance. The dropout rate is 40.7-68%. However, most patients stop treatment during the first 2-3 months. In comparative studies, alprostadil has a low treatment interruption rate compared to all drug combinations (37.6%).

Today, intraquernosal pharmacotherapy is considered a second-line therapy. Patients not responding to oral therapy can be subjected to intracavernous injections with high success rate (85%).

Penile prostheses. Surgical implantation of a prosthesis may be indicated in patients who have not responded to pharmacotherapy or in those who prefer a permanent solution to ED. There are two types of prostheses: malleable (semi-rigid) and inflatable (two- or three-component) [4]. (Figure 1.5)

Most patients prefer tri-component inflatable devices as they provide a more "natural" erection. However, 2-component inflatable prostheses can be reliable with fewer mechanical complications and a simple implantation technique. Semi-rigid prostheses provide permanent penile rigidity and may be chosen by older patients with infrequent intercourse. Inflatable prostheses are much more expensive [9].

Prosthesis implantation is one of the highly effective treatments for ED with a success rate of 70-87%

It is well known that treatments for ED should have a predictable onset of action, a sufficient duration of effect for sexual activity, be safe and well tolerated. In accordance with the recommendations of the European Association of Urology, the drugs of choice in the treatment of ED are phosphodiesterase type 5 inhibitors (PDE5). However, in 30-40% of applications they are ineffective. There is evidence that patients who do not respond to the first use of PDE5 inhibitors often do not respond properly to repeated doses. It should be noted that patient preferences play a key role in the choice of treatment method and group of drugs, in addition, the individual needs of patients are diverse, therefore.

Researchers have started developing alternative methods of treatment and administration of drugs for ED. Intranasal use of drugs.

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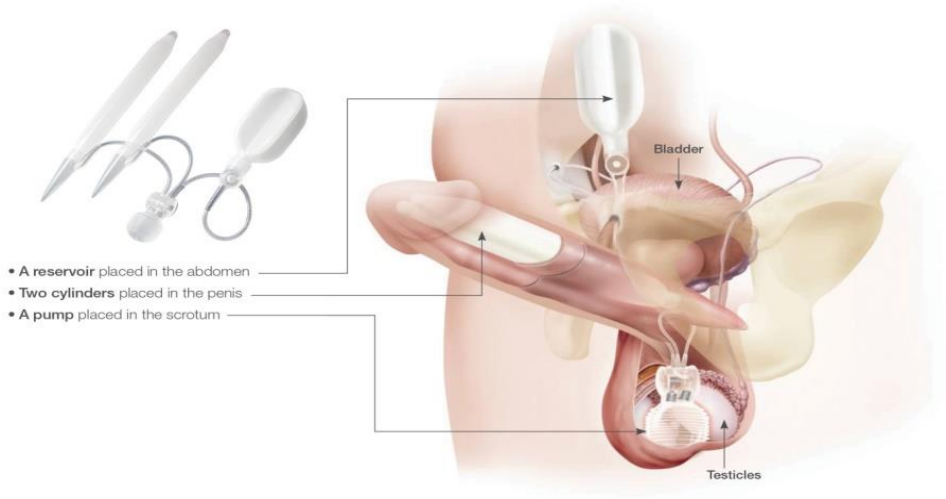

Over the past three decades, the nasal mucosa has been recognized as a therapeutically effective alternative route for drug administration. In rat studies, Hussain al. [9], showed that the nasal route of administration of propranolol in terms of absorption was comparable to intravenous administration. The nasal route of administration received additional attention after a workshop organized by Dr. Y.E. Chien in 1984 [7]. The workshop entitled "Intranasal Prescribing for Systemic Drugs" provided a comprehensive overview and guidelines for researchers in this field. The interest of researchers in the nasal method of administration is explained by the high degree of blood supply and the permeability of the nasal mucosa. Kolliker [5] in 1852, Kohlrausch [6] in 1853, and Zuckerkandl [7] in 1884 found a rich capillary network in the subepithelial zone and around the nasal glands, and a cavernous plexus deeper than the glandular zone. Further, only in 1935, additional information was obtained in this area. [7,8]. Several researchers have studied the anatomical and physiological aspects of the structure of the nasal mucosa, including the characteristics of the vascular system in relation to drug administration. [5,9,6]. The nasal cavity is abundantly supplied with blood. The mucous membrane of the nasal cavity can be divided into 2 types: the olfactory part (olfactory) and non-olfactory (non-olfactory). The olfactory epithelium is a multi-row columnar structure. It consists of specialized olfactory cells, supporting cells, serous and mucous glands. The non-olfactory part is a vascular membrane, the surface of which is covered with ciliated multi-row columnar epithelium. Arterial blood supply is provided by the internal and external carotid arteries. The vascular nature of the nasal mucosa, together with low barrier properties to drug penetration, makes the nasal route of administration attractive for the administration of many drugs, both peptide and non-peptide. In addition, the olfactory region provides the potential benefit of drug action via neurons, which may facilitate their access to the cerebrospinal fluid when administered nasally.

Advantages and disadvantages of the nasal route of drug administration

It is recommended that a penile prosthesis be used as the third line of treatment for patients with ED. With the ineffectiveness of conservative therapy for ED, which is manifested by the absence of positive clinical dynamics and an increase in scores during repeated questioning according to the IIEF (IIEF) or IIEF-5 (SHIM) questionnaires, as well as if the patient wishes, the optimal treatment is the implementation of penile prosthesis. There are two types of penile implants: flexible (semi-rigid) and inflatable (two or three-piece hydraulic systems). Most patients prefer three-piece prostheses due to the achievement of a more natural erection. Satisfaction with sexual life after their implantation is noted by over 90% of the operated patients and their partners. Two-piece inflatable prostheses are more often used by surgeons with relatively less experience in the operations discussed, due to the absence of the need for a reservoir implantation fraught with complications (as with the introduction of three-piece implants). A semi-rigid penile prosthesis creates a permanent axial rigidity of the penis. Phalloprosthesis is carried out through 3 operational accesses: scrotal, subpubic and coronal. The scrotal access provides good visualization, allows, if necessary, to approach the proximal part of the penis pedicles, avoiding damage to the dorsal nerves, with the possibility of installing a pump under visual control. With concomitant severe urinary incontinence, an artificial sphincter of the bladder can be simultaneously installed through the same access. With this access, the

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reservoir is installed in the retropubic space without visual control, which can be fraught with damage to the bladder and iliac vessels in patients who have had a history of major operations on the pelvic organs (radical prostatectomy or cystectomy).

In such situations, it is safer to resort to an ectopic axillary reservoir placement over the transverse fascia of the abdomen through the main skin incision. The subpubic approach offers the advantage of vision-guided reservoir placement, but pump implantation can be difficult and is associated with an increased risk of damage to the dorsal nerves of the penis. Coronal access is preferable in situations where ED is combined with a severe deformity of the penis (in Peyronie's disease) for simultaneous corporoplasty or, if the patient wishes to increase the length of the organ during penile prosthesis (folding technique).

The most severe complication of penile implants is periprosthetic infection. Its frequency is significantly lower in frequently operated surgeons. Currently, penile prostheses with an antibacterial coating are increasingly being used, which can reduce the likelihood of this complication from 5% to 2%. The service life of modern penile implants exceeds 15 years. With their mechanical failure, a new phalloprosthesis is reimplanted.

It is recommended that patients after radical prostatectomy begin penile rehabilitation early after surgery. Level of persuasiveness of recommendations A (level of evidence - 1)

Lifestyle normalization and modification of risk factors in patients with ED are recommended as possible prevention measures in patients with erectile dysfunction.

Normalization of lifestyle, sufficient physical activity, exclusion of smoking, limiting alcohol consumption, control and correction of body weight, glucose and lipids in the blood, as well as regular sex life.

The nasal route of administration is an alternative for the administration of many medicinal agents and has the following advantages:

– Rapid absorption, high bioavailability, resulting in a reduction in the dose of the drug
– rapid onset of therapeutic action
- exclusion of the influence of the first passage of the drug through the liver
- exclusion of gastrointestinal metabolism
- exclusion of the irritating effect of the drug on the gastrointestinal tract
– reduced risk of overdose
– non-invasive, therefore no risk of infection
– ease of use and the possibility of simple self-application by the patient
– greater patient compliance
– can be an addition to existing pharmaceuticals

The nasal route of administration is, of course, not applicable to all drugs. Despite the high permeability of the nasal mucosa, many drugs cannot be absorbed in sufficient quantities. Insufficient water solubility of drugs is also often a problem. Some drugs may cause mucosal irritation, others may be metabolically degraded in the nasal cavity. The nasal route is less convenient for long-term drugs. For example, insulin for the treatment of type 1 diabetes may not be a candidate for nasal administration, as patients require daily administration for the rest of their lives. The nasal route of drug administration may be acceptable if the long-term drug is prescribed less frequently. Drugs requiring constant blood concentrations should not be considered for nasal use, as there is no generally accepted method for developing extended release nasal formulations.

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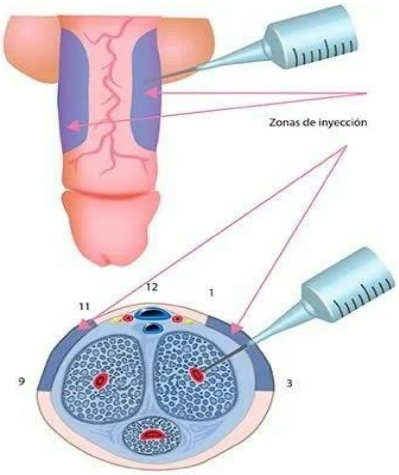

The molecular weight of the studied drugs ranged from 190 to 70,000. Based on their results, they hypothesized that nasal absorption of water-soluble compounds occurs through water channels between mucosal cells, which limit permeability according to the size of the molecules.

Several studies have shown the effect of the dose of drugs on nasal absorption [7] In general, higher levels of absorption were observed with increasing dose of the substance. But it is important to note how doses vary. If the dose is increased by increasing the volume of the drug, then there may be a limitation - to what extent nasal absorption can be increased. The nasal cavity can retain only a limited amount of substance, above which the drug will be removed from the nasal cavity. The ideal volume of a substance varies from 0.05 to 0.15 ml with an upper limit of 0.2 ml.

In adults, the nasal cavity is divided by a mucous membrane 2-4 mm thick (162). surface about 180. sm. The mucosal vessels are surrounded by adrenergic nerves acting as alpha-adrenergic receptors. Stimulation of these receptors reduces blood flow in animals and humans and vice versa. The deposition of the drug in the anterior part of the nasal cavity ensures a longer stay of the drug in the nasal cavity and, accordingly, a longer period of drug contact with the mucosa. With deposition in the back, the drug is more quickly excreted from the nasal cavity through mucociliary clearance. The permeability of the posterior part of the nasal cavity is higher than that of the anterior part.

Based on a review of the literature, the ideal candidate for nasal application should have the following properties:

Adequate solubility to ensure compliance with the desired dose of 0.025-0.15 milliliters of solution per nostril, adequate absorption properties for nasal application lack of irritative properties stability appropriate rationale for nasal formulations, eg rapid onset of action low dose. [7,8]

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