УДК: 616.69-008.3-08-039.73

Cold-sensitive thermo-TRP-channels as possible target in treatment of premature ejaculation: pilot study

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An open-label study of the effect of TRPaZS-1 – TRP8 channel activator in gel form in 33 patients with lifelong premature ejaculation. Demonstrated:
1. TRP8 ion channel activator TRPaZS-1 is a promising tool for the treatment of premature ejaculation, which is able to improve statistically and clinically significant parameters of ejaculatory function, as well as erection, libido and orgasm, while reducing the severity of psycho-emotional distress.
2. TRPaZS-1 has an acceptable safety profile because it has no systemic adverse effects, and the local ones have a low intensity, are short-lived, and in most cases presented with a feeling of heartburn on the penis.
3. Further studies of the receptors of the penis head, the role of TRP8 ion channels in their functioning, and possible substances for modeling the activity of these channels are needed.
Key words: *lifelong premature ejaculation, local therapy, receptors of the glans penis, cold sensitive TRP8 ion channels, cooling agent.*

Холодові термо-TRP-канали як можливі мішені в лікуванні пожиттєвої передчасної еякуляції: пілотне дослідження

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Проведено відкрите дослідження впливу активатору іонних каналів TRP8 TRPaZS-1 у формі гелю у 33 пацієнтів з пожиттєвою передчасною еякуляцією. Продемонстровано:
1. Активатор іонних каналів TRP8 TRPaZS-1 є перспективним інструментом для лікування передчасної еякуляції, що здатен поліпшити статистично та клінічно значущі параметри еякуляторної функції, а також ерекції, лібідо та оргазму, зменшуючи при цьому тяжкість психоемоційного дистресу.
2. У TRPaZS-1 – прийнятний профіль безпеки, оскільки він не має системних негативних ефектів, а місцеві мають низьку інтенсивність, є короткочасними і в більшості випадків представлені відчуттям печії на голівці статевого члена.
3. Потрібні подальші дослідження рецепторів голівки статевого члена, ролі іонних каналів TRP8 у їхньому функціонуванні та можливих речовин для моделювання активності цих каналів.
Ключові слова: *пожиттєва передчасна еякуляція, місцева терапія, рецептори статевого члена, холодочутливі іонні канали TRP8, охолоджуючий агент.*

Холодовые термо-ТРП-каналы как возможная мишень в лечении преждевременной эякуляции: пилотное исследование

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Проведено открытое исследование влияния активатора канала TRPaZS-1-TRP8 в форме геля у 33 пациентов с врожденной преждевременной эякуляцией. Продемонстрировано:
1. Активатор ионных каналов TRP8 TRPaZS-1 является многообещающим инструментом для лечения преждевременной эякуляции, который способен статистически и клинически значимо улучшить параметры эякуляторной функции, а также эрекцию, либидо и оргазм, уменьшая при этом тяжесть психоэмоционального дистресса.
2. У TRPaZS-1 – приемлемый профиль безопасности, поскольку он не имеет системных побочных эффектов, а местные имеют низкую интенсивность, непродолжительны и в большинстве случаев проявляются чувством жжения на головке полового члена.
3. Необходимы дальнейшие исследования рецепторов головки полового члена, роли ионных каналов TRP8 в их функционировании и возможных веществ для моделирования активности этих каналов.
Ключевые слова: *преждевременная эякуляция, местная терапия, рецепторы головки полового члена, чувствительные к холоду ионные каналы TRP8, охлаждающий агент.*

Premature ejaculation (PEj) is the most common sexual dysfunction in men, for which, unlike erectile dysfunction, an acceptable method of pharmaceutical correction has not yet been developed. Each of the two main therapeutic strategies used in PEj has significant drawbacks. Since along with ejaculation, serotonin also regulates a number of processes in the nervous system, the blockade of the reuptake of this mediator from the synoptic cleft can lead to undesirable effects such as decreased libido, worsening of erection, mood disturbance, and headache [1]. In turn, desensitization of the glans penis by means of lidocaine / prilocaine negatively affects the extent of pleasant sensations during intercourse and can also compromise an erection [2].

Nevertheless, the development of local pharmacotherapy for PEj remains attractive, since it is devoid of systemic side effects, can be used «on demand» and quickly show the effect [2].

In one of the works devoted to the use of a low-energy laser for the treatment of persistent penile anesthesia caused by serotonin reuptake inhibitors, the authors [3] suggested the importance of cationic transient receptor potential (TRP) ion channels in the functioning of mechano-, thermo- and chemosensitive

Table 1

Calculated values of the criterion W (sum of ranks before and after treatment) in comparison with $W_{critical}$

Parameter	W calculated	Wcritical (n=33, p=0,05)
Duration of pre-ejaculatory interval	645	187
Control over ejaculation	561	187
Distress	569	187
Erection	670	187
Libido	434,5	187
Orgasm	561	187

nerve endings and receptors of the glans penis.

In the field of our interest were TRP channels type 8, which are activated by cold temperature and cooling agents. We hypothesized that the application of a cooling agent on the skin of the glans penis before intercourse should improve patient control over the ejaculation.

PATIENTS AND METHODS

After signing informed consent, 33 patients with lifelong PEj (according to ISSM evidence-based updated definition) aged 21–33 years and in stable sexual relationships (duration not less then 6 month) were included. Experimental treatment: small amount of the gel, containing 10% of TRP channels type 8 activator – TRPaZS-1 should be applied to the glans penis and foreskin 1 hour before sexual intercourse. Treatment period planned to last 1 month. For this period each patient should have not less than 4 attempts of sexual intercourse.

Before starting treatment and on the day the intercourse being performed with using experimental gel patient should complete questionary, assessing all parameters of male sexual function (libido, erection, ejaculation (duration of pre-ejaculatory interval, control over ejaculation), orgasm) as well distress, associated with PEj, by means of visual analog scale (0–10) that is intuitively clear for a patient. Information as to character and duration of sensations after gel application were also collected by means of specially designed questionary. The nature, severity, date / time of occurrence and duration of adverse events were recorded by the patient in a special diaryData distribution was described with median and percentiles – Me (Percentile 25, 75). Statistical significance of median differences were assessed with Wiilcoxon test. Significance level 0,05.

RESULTS

100% of patients completed the study. During treatment period most of them performed from 5 to 7 sexual intercourses (Me = 6). Analysis of patient distributions according to initial subjective estimates of the parameters of the ejaculatory function (duration of the pre-ejaculatory interval, level of control of the moment of the ejaculation) revealed that most of them were grouped around 2 points – a marked decrease of the parameter (Fig. 1, 2). They also predominantly grouped around 8 points of the degree of distress, indicating on the presence in most of them of pronounced psycho-emotional disorders, associated with PEj. (fig. 3). It is important that in most patients, a moderate worsening of erection (median – 5 points), as well as a decreasing of libido (median – 6 points) and orgasm (median – 7 points) were noted (Fig. 4–6).

The use of gel TRPaZS-1 influenced the distribution of patients in all studied parameters. In particular, according to the duration of the pre-ejaculatory period and the degree of control, patients began to concentrate around 6 points, i.e., the severity of these parameters changed from low to moderate. In turn, the correction of ejaculatory function contributed to a decrease in the severity of distress: its median changed from 8 to 3 points. Positive changes also occurred in the indices of erection (increase in median from 5 to 7 points), libido (from 6 to 8 points) and orgasm (from 6 to 8 points). Further comparison of the calculated values of the Wilcoxon criterion (*W*) with a critical value allows us to

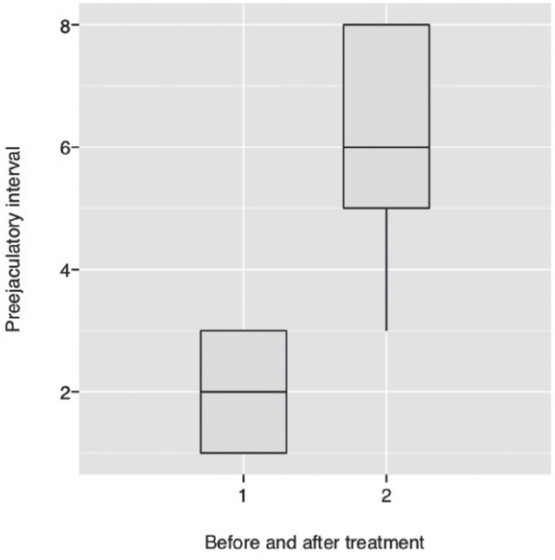

Fig. 1. The effect of the gel TRPaZS-1 on the distribution of patients as to preejaculatory interval

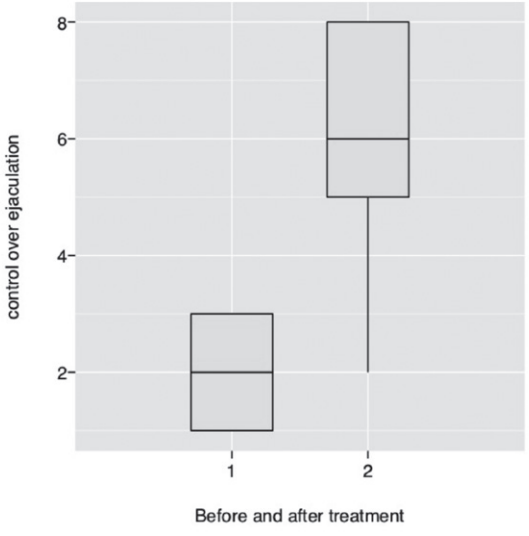

Fig. 2. The effect of the gel TRPaZS-1 on the distribution of patients as to control over ejaculation

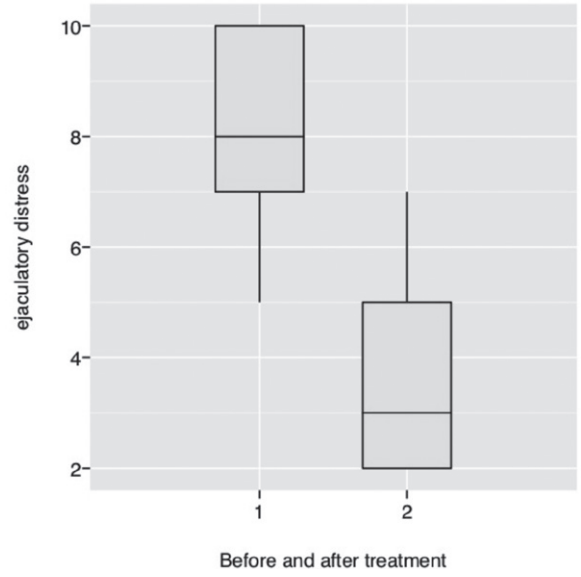

Fig. 3. The effect of the gel TRPaZS-1 on the distribution of patients as to control over ejaculation

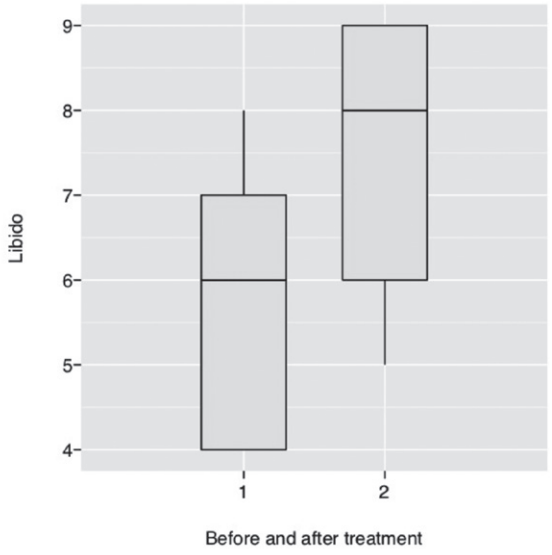

Fig. 4. The effect of the gel TRPaZS-1 on the distribution of patients as to libido

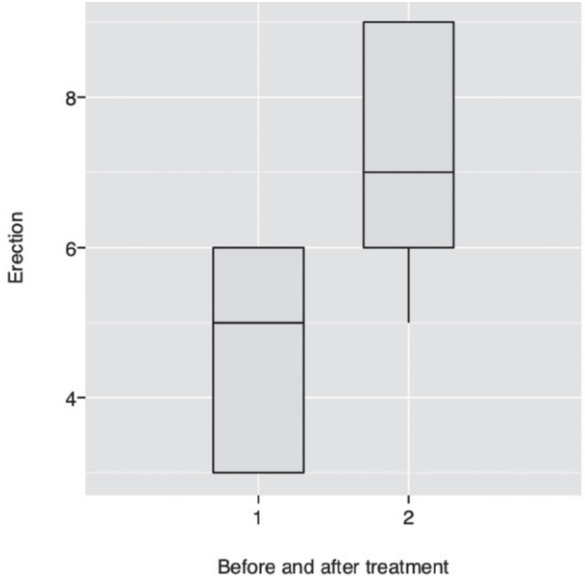

Fig. 5. The effect of the gel TRPaZS-1 on the distribution of patients as to erection

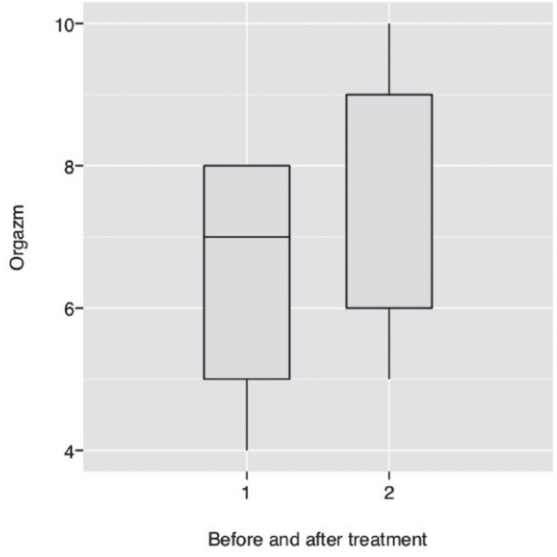

Fig. 6. The effect of the gel TRPaZS-1 on the distribution of patients as to orgasm

conclude that the listed changes registered after application of the gel are nonrandom (Table 1)

Despite 100% of the patients reported local adverse events most of them were mild or mild-to-moderate. According to the frequency of occurrence, these phenomena were distributed as follows: burning on the glans penis – 81,8%, a feeling of cold – 75,7%, numbness – 12,1%. The median of duration of these phenomena was 20 (15;32) min, they did not require additional treatment and resolved before penetration.

DISCUSSION

The participation of TRP ion channels in the functioning of sensory neurons allows us to consider them as potential targets in the treatment of PEj [4]. However, the development of this concept is hindered by the fact that so far not only the role of these channels in the pathogenesis of premature ejaculation has not been studied in detail, but also the role of specific types of receptors of the glans penis in the formation of pleasant sensations during intercourse. In fact, a search in Medline revealed only two articles on the study of penile receptors in humans and one in rats. Thus, in histological and immuno-histochemical studies of cadaveric material and material obtained after circumcizion, Meissner and Pacini bodies were identified, with a density of 1-3 receptors in the field of view at a 100-fold increase [5–7]. It should be noted that these data were obtained on a small number of objects. We also found only one work that pointed to the possible role of TRP ion channels in desensitization of the glans penis in patients taking SSRI [3].

The possibility of activating the transient receptor potential TRP8 ion channels with cooling agents allowed us to formulate

a hypothesis according to which applying such an agent to the glans penis should reduce the intensity of afferent impulse to the spinal centers and, thus, increase the duration of the pre-ejaculatory period and the patient's ability to control the moment the onset of ejaculation. As a cooling agent, we used TRPaZS-1 gel, which the patient had to apply 1 hour before the silt act. This time was chosen inherently to reduce the severity of local adverse events.

As our work has demonstrated, applying a cooling gel to the glans penis statistically and clinically significantly improved both the subjective assessment of the duration of the pre-ejaculatory and the ability to control the moment of ejaculation (increase in median from 2 to 6 points).

Another important finding of our study is the establishment of the fact that the activation of TRP8 ion channels by cooling agent not only did not negatively affect erection, libido and orgasm, but also improves them. In particular, at the end of the study, statistically significant increases in these domains were registered. Cooling agents differ significantly from these effects from local anesthetics.

Another important aspect of the use of cooling agents in premature ejaculation is their safety. As our study showed, TRP8 ion channels activator TRPaZS-1 does not lead to systemic adverse events. On the other hand, local adverse events, including burning, a feeling of cold, numbness, have insignificant intensity and duration and did not require additional treatment.

The limitations of our study include open design, a small sample size, and the absence of a control group. Also, in order to facilitate the process of obtaining a subjective assessment of the parameters of sexual function from the patient, we used more understandable and demonstrative but not standardized visual analogue scales.

CONCLUSION

1. TRP8 ion channels activator TRPaZS-1 is a promising tool for the treatment of PEj capable to improve statistically and clinically significant parameters of ejaculatory function as well as erection, libido and orgasm, while reducing the severity of psycho-emotional distress.

2. TRPaZS-1 has an acceptable safety profile, since it does not have systemic negative effects, and local ones have low intensity, are short-term and in most cases are represented by burning on the gains penis.

3. Further studies of the receptors of the glans penis, the role of TRP8 ion channels in their functioning and possible substances for modeling the activity of these channels are needed.

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Статья поступила в редакцию 23.12.2019