Contraception

Rapid assessment of the clinical status and metabolic profile of female cats with different methods of sexual function regulation

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Introduction

According to the analytical agency Dalia Research in February 2017, about 33% and 23% of worldwide population, respectively, keep dogs and cats at home; when it comes to Russia, the cat is the most popular pet. Cats are present in more than half of households, and about 20% of owners keep several cats [1]. The problem of undesirable behavior of female cats during estrus is familiar to every owner; it causes serious inconvenience and reduces the pleasure of communicating with the animal [2-4]. Options for correcting behavioral manifestations associated with the natural implementation of their reproductive function by the cats include oral hormonal contraceptive drugs (HCD) and neutering. We will briefly discuss each of these options. Currently, the following drugs for regulating the sexual behavior in female cats are presented on the Russian market: mono-hormonal drugs, the active substance of which is a synthetic analog of progesterone (megestrol acetate, medroxyprogesterone acetate) in a high dosage, and more modern low-dose bi-hormonal drugs, the active substances of which create a combination consisting of gestagen (mepregenol in the form of a complex ester) and ethinyl estradiol in a certain ratio [5], which provides a fast, effective and safe correction of estrous behavior [6]. It should be noted that the effect of HCD on the animal body is reversible, which is especially important for cat owners who, for one reason or another, are not ready for a surgical solution of the problem under discussion or are not interested in the offspring at the present moment. The use of gestagen-containing mono-hormonal drugs in the veterinary medicine of small domestic animals, despite the use of the hormone in doses which are considered effective and safe, however, is often accompanied by reports on undesirable side effects. Nevertheless, transition to using modern synthetic progestins, devoid of androgenic, estrogenic, anabolic, gluco-and mineralocorticoid, antiestrogenic and thymolytic effects which are typical for classic gestagens (megestrol etc.), can make the discussed problem of side effects less topical. It is especially possible when the degree of efficacy and safety of used progestins is high enough, and the used doses are minimal due to the synergy with estrogen, which is implemented in bi-hormonal contraceptive drugs (BCD), an example of which is the drug Sex Barrier. Hormonal drugs are used in two ways: to maintain the cat in a state of sexual abstinence and for situational interruption of the initiated estrus. For the most secure and effective administration, these drugs are used in accordance with the instructions for clinically healthy cats, starting from the 2nd estrus, otherwise their effectiveness and safety are not guaranteed. Spaying (ovariohysterectomy, OVH) is irreversible surgical intervention, a routine operation in the practice of a general veterinarian, which, however, is a certain stress for the animal, carries risks of developing certain complications, and there is a need for special care, time and money expenditures during the postoperative period. Veterinarians and owners should also keep in mind that OVH does not

provide a 100% guarantee in solving the problem of estrus in female cats, and confirmation of this thesis will be provided below.

After spaying, there is a change in the hormonal status of the animal, resulting in a decreased energy consumption, and without correcting the diet composition and its caloric value it can lead to obesity and other metabolic diseases, reduce the duration and quality of life of the female cat [6-8]. There exists a very common opinion among the veterinarians and cat owners that surgical neutering is a safer and more reliable approach compared to the use of HCD, which allows to radically eliminate undesirable manifestations of estrous behavior in animals and to protect them from diseases of the mammary glands, uterus and ovaries. Other owners and veterinary specialists consider the use of HCD at least as effective, but at the same time reversible, simpler, more affordable and safer method of suppressing sexual cyclicity. Due to the lack of scientific data on the proper long-term use of HCD, there is a continuing debate among veterinarians and owners whether the long-term use of hormonal contraceptives contributes to the development of severe complications from both genital and extragenital spheres of the cat's body. A recently published study assessing the effect of the bi-hormonal contraceptive drug (BCD) Sex Barrier on the body of cats (over two years of use) did not reveal deviations from the physiological normal range according to the results of clinical, laboratory and instrumental diagnostics [9]. If the data on the effect of neutering and the effect of mono-hormonal contraceptives on the metabolism of cats are presented in the works of domestic and foreign researchers [10-13], the impact of BCD on the body is sufficiently covered only in human's medicine [14]. This is associated with their relatively recent appearance on the Russian veterinary market, a lack of clinical trials and a limited number of manufacturers of such drugs. In this regard, objective of this work was to conduct a comparative rapid assessment of the impact of a long-term household use of BCD Sex Barrier and neutering on the clinical status, hematological and biochemical parameters of the cats. This study will make a certain contribution to the collection of scarce data on the safety assessment of a long-term use of BCD by owners at home. It will also contribute to the shift of the paradigm about the harm of hormonal contraception for the genital and extragenital sphere in cats to a more reasoned approach when choosing a particular option for regulating sexual behavior in female cats.

Materials and methods

The study was conducted during the period from September 2016 to May 2017 in the veterinary clinic Bio-Vet (Moscow). Senior executive was a Head of Laboratory Diagnostics Department, doctor of veterinary science E. E. Belova. The effects of a long-term use of the drug Sex Barrier and neutering on the clinical status and metabolic profile of cats were studied using two approaches: a prospective and retrospective study. A prospective study was conducted to objectively assess the condition of the animal at the time of referral to the clinic. A retrospective study was used to test etiological hypotheses. In total, the experiment included 90 cats of different breeds aged from 2 to 8 years old, whose owners applied to the veterinary clinic for a scheduled annual vaccination of the animal. According to the inclusion criteria, the animals were divided into three groups based on the anamnestic data. Group 1 included cats spayed at the age of 1-2 years old (30 animals); group 2 included cats who at the time of the study have been receiving the drug Sex Barrier (drops) at home for 2-6 years (30 animals); group 3 was a control group which consisted of animals who were not subjected to any methods of regulating sexual behavior (30 animals). Active pharmaceutical substances of the drug Sex Barrier (LLC Research and Production Company Skiff, Moscow) in the form of drops for oral use are mepregenol acetate, water-soluble, and ethinyl estradiol (in the ratio of 100:1); 1 ml of the drug contains 1 mg of water-soluble mepregenol acetate and 0.01 mg of ethinyl estradiol. According to the degree of impact on the body, the drug belongs to low-hazard substances (hazard class IV according to GOST 12.1.007-76) [15]. The following parameters were registered in all cats included in the study: age, breed, body weight, the state of hair and skin, teeth, oral mucosa, ear shells and mammary glands. On the day of referral, blood was drawn from the animals for clinical and biochemical screening. The following parameters in the complete blood count were

tested: hematocrit, hemoglobin, red blood cells, white blood cells, and platelets. The following parameters were tested in the biochemical blood assay: bilirubin, aminotransferases, alkaline phosphatase, GGT, urea, creatinine, amylase, glucose, LDH, total protein, cholesterol. Additionally, the concentration of anti-Mullerian hormone (AMH) in the blood was determined in spayed cats in the Invitro laboratory via the ELISA method using Beckman Coulter kits in order to rule out the ovarian remnant syndrome (ORS) as a complication of surgical spaying. The results of the study were processed via BioStat 3.03 program software.

Results and discussion

When collecting anamnestic data, it was determined that four (13%) of the original 30 spayed female cats enrolled in the study had estrus once again during different time periods after the operation; it was registered by their owners. In this regard, the concentration of AMH was determined in group 1 as a marker of the presence of residual ovarian tissue. The results of the analysis showed that 26 spayed female cats that did not show signs of estrus after surgical removal of the uterus and ovaries have a low content of AMH in the blood serum (less than 0.1 ng/ml), which coincides with the data known from the literature [16, 17]. In four cats with recovered sexual cyclicity after the surgery, AMH content was by an order of magnitude higher than in the rest of the spayed animals. It constituted 1.34±0.03 ng/ml, which in combination with behavioral signs of estrous behavior, indicated development of the ovarian remnant syndrome (ORS) [17]. Verified diagnosis excluded further participation of these animals from the study, and, accordingly, 26 animals were further studied in the first group. Another factor that attracted attention during the clinical examination of the animals was the obvious difference in the body weight of cats belonging to different groups. Thus, 17 out of 30 (56%) cats after OVH had excessive body weight (table 1), while in the group of animals receiving the drug Sex Barrier, and in the control group of cats, obesity was not registered. The fact that more than half of the spayed cats are obese is consistent with the results of studies that have established a direct relationship between OVH and subsequent development of obesity [6-8].

Body weight of female cats involved in the study

Group	The number of female cats with excessive body weight	Median body weight per group, kg
№1 OVH	17	4,444±0,226***
№2 «Sex Barrier»	0	3,210±0,132
№3 Control	0	3,061±0,178

*** – significant, $p<0.0001$

According to the results of examination and determination of body weight of spayed female cats, no other deviations from the target physiological normal parameters were registered in animals who have been receiving Sex Barrier for a long time and control cats. Table 2 demonstrates the results of a complete blood count test in female cats of the studied groups. The obtained data allow us to conclude that hematocrit, hemoglobin concentration, number of red blood cells, white blood cells and platelets in cats of all groups did not have significant differences and remained within the reference values. This indicates that OVH and a long-term use of the drug Sex Barrier do not negatively affect morphological parameters of the blood. The results of blood biochemistry in female cats after ovariohysterectomy and in female cats receiving Sex Barrier are presented in table 3. As follows from the data presented in the table, most of the parameter of protein, lipid and carbohydrate metabolism determined during the study in female cats from all groups were within the physiological normal limits. Deviations from the reference values and from the parameters of the other two groups were detected in the content of cholesterol and AST in female cats that underwent surgery. At the same time, it should be noted that the registered increase in cholesterol levels as compared to the cats who have been receiving Sex Barrier for a long time and control animals (which is an indication of changes in lipid metabolism) is fully consistent with the established fact of obesity in most animals from the group of spayed animals.

A slight increase in AST activity, which is a non-specific enzyme found besides liver in red blood cells, myocardial cells, kidneys, and muscles, in spayed cats does not indicate any functional changes in the organ and has no diagnostic value without a significant proper and simultaneous (2-3-fold) increase of other parameters of extra - and intracellular metabolism of hepatocytes.

Table 2. Complete blood count parameters in female cats

Parameter	Group			Reference interval[1]
	№1 OVH	№2 «Sex Barrier»	№3 Control	
Hematocrit, %	44,8±6,78	47,6±5,18	39,0±7,25	26–48
Hemoglobin, g / l	106,0±29,28	112,0±27,4	128,0±31,61	80–150
Erythrocytes, 10^{12}/l	9,85±1,0	8,7±1,4	7,7±2,27	5,3–10,0
Leukocytes, 10^9/l	16,06±11,66	8,18±6,72	10,31±7,13	5,5–18,5
Platelets, 10^9/l	331±113,48	365,0±98,15	423,0±154,0	300–630

[1] Reference interval of the veterinary laboratory Aibolit-Lab

Table 3. Blood biochemistry parameters in female cats

Parameter	Group			Reference interval[1]
	№1 OVH	№2 «Sex Barrier»	№3 Control	
Total bilirubin, μmol / l	7,28±0,30***	8,18±0,54	9,74±0,64	3,0–12,0
Direct bilirubin, μmol / l	2,80±0,13**	3,36±0,19	3,78±0,19	0,0–5,5
AST, U / L	44,45±5,90	30,89±2,69	30,81±3,66	9–29
ALT, U / L	58,07±4,50*	61,9±5,8	52,88±3,7	19–79
ALP , U / L	59,6±5,79	58,19±6,32	56,98±3,97	39–120
GGT, U / L	2,79±0,18	2,06±0,29	2,38±0,41	1,0–10,0
Creatinine, μmol / L	156,26±5,47	143,79±5,02	118,0±5,24	70–165
Urea, mmol / l	9,7±0,44***	10,85±0,77	10,42±0,42	5,4–12,1
α- Amylase, mmol / l	1023,70±71,50	1212,06±52,74	982,0±75,37	500–1500
Glucose, mmol / l	7,17±0,61	7,14±0,42	6,43±0,37	3,3–6,3
ЛДГ, Ед/л	180,50±16,61*	229,0±19,76	145,0±11,62	50–495
Total protein, g / l	70,70±0,96**	65,11±1,15	65,65±1,50	54–77
Cholesterol, mmol / l	4,21±0,26*	3,08±0,10*	2,88±0,15*	1,6–3,7

[1] Reference interval of the veterinary laboratory Aibolit-Lab

Note. * – significant, $p<0.05$ ** – significant, $p<0.001$*** – significant, $p<0.0001$

Thus, there were no serious abnormalities in the clinical status and metabolic profile of female cats with OVH, excluding four animals with ORS, except for development of obesity, which correlated with an increase in cholesterol levels. Observed changes should be taken into consideration by veterinary specialists and owners of sterilized cats to prevent metabolic disorders after surgery. Based on the obtained results, it can be concluded that long-term use of the drug Sex Barrier by owners in household conditions according to the schemes for terminating

and delaying estrus does not change the clinical status, body weight, basic hematological parameters and biochemical metabolic markers. This allows us to recommend the use of bi-hormonal contraceptives for regulation of the reproductive cycle as a reversible, safe and effective alternative to neutering, which is not a 100% solution to the problem of unwanted estrus manifestations in female cats.

Conclusion

A rapid assessment of the clinical status and metabolic profile of spayed female cats and cats who have been receiving BCD Sex Barrier for a long time in domestic conditions has been carried out. The obtained data demonstrated the presence of excess fat in more than half of spayed cats, as well as a significant increase in cholesterol levels in this group of animals. This was not observed in animals receiving a bi-hormonal contraceptive drug. There is no doubt that current approaches of modern veterinary medicine can correct these and other complications that occur after the neutering. However, one must remember that the operation involves a certain probability of developing some complications associated with anesthesia and bleeding, stress and rehabilitation, significant additional financial and time expenditures, as well as possible reduction in the quality and life expectancy of the animal in the long term prospective. Probable development of the ORS also determines the need for a more balanced, and in some cases individual approach to choosing the option for controlling estrus in female cats. Surgical treatment of ORS in practice is extremely rare due to the difficulties of establishing the localization of residual ovarian tissue. In addition, repeated surgical intervention carries additional operational and postoperative risks. The conservative method of treatment for this syndrome is the long-term use of oral HCD.

It is also important to note that in contrast to the standard procedure of surgical spaying, hormonal regulation of the reproductive function of female cats is a more personalized approach to each individual animal. A simple procedure of administering HCD to the animal at home, if the owner complies with the instructions for use, makes the use of bi-hormonal drugs maximally safe for the animal and convenient for the owners. Thus, today the competent use of HCD is the most humane, physiological, safe and effective method that allows the owner to reversibly regulate the sexual function in female cats.

Conflict of interests

The manufacturer of the drug Sex Barrier® and the program of this study is LLC Research and Production Company SKiFF. The decision to publish the results of scientific work and the rights belong to the developer LLC Research and Production Company SKiFF.

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