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Expression of the multidrug resistance gene (MDR1) and microRNAs in canine transmissible venereal tumors

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Abstract

The multidrug resistance gene (MDR1) is responsible for encoding P-glycoprotein. This protein is located in the cell membrane, distributed throughout different tissues and physiological barriers. Therefore, the objective of this study was to determine the expression profile of the multidrug resistance gene (MDR1) and microRNAs 126 and 214 in dogs with and without transmissible venereal tumor (TVT). Samples from 18 dogs mixed breed at different ages and from both sexes were analyzed: 9 samples were neoplastic tissue obtained by biopsy from dogs with TVT, diagnosed by imprint cytology, and 9 samples of skin from abdominal and pre-scrotal region obtained from dogs undergoing elective castration at the Zoonosis Control Center. The samples originated from the state of Pará, Brazil. Sample processing was performed in laboratories at the Federal Rural University of the Amazon. RNA extraction was performed using the Trizol® method, gene and microRNA expression was evaluated by qRT-PCR; cytology analyses were also performed. Gene expression of the MDR1 gene was observed to be ten times higher in the test group compared to the control group ($P<0.05$). The expression of microRNA-214 was reduced ($P<0.05$) in the test group, while microRNA-126 showed no significant difference between the groups. These results demonstrate that high MDR1 expression is observed in dogs with TVT, regardless of the cytological type evaluated, while low expression of microRNA-214 indicates a possible tumor suppressor role in this neoplasm. Additional studies are needed to investigate the relationship between gene expression, drug resistance, and regional variations.

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Introduction

Transmissible venereal tumor (TVT) is a round cell neoplasm transmitted between dogs primarily during copulation through the direct implantation of tumor cells. It can be found in the external and internal genitalia, and occasionally in extragenital locations (1). Chemotherapy is the treatment of choice, with high cure rates and applicability in metastatic and multifocal cases. However, multidrug resistance (MDR) is a significant challenge and can arise during treatment or in cases of relapse (2).

The multidrug resistance gene, called MDR1 or ABCB1, is the gene involved in cases of cross-resistance of cells to multiple drugs. It is a gene that encodes P-glycoprotein, which prevents various drugs from entering cells (3). Some studies were conducted evaluating the MDR1 gene in dogs with neoplasias, MDR1 expression was measured in blood samples from dogs with lymphoma, before and after chemotherapy (4), MDR1 gene expression was also measured in tissues from healthy dogs and dogs with lymphoma (5), and expression of this gene in cells from dogs with TVT after chemotherapy (6).

Just as MDR1 has the ability to influence chemotherapy treatment, microRNAs, which are small RNAs, are currently gaining prominence as non-invasive cellular and molecular biomarkers with potential for prediction, diagnosis, prognosis, and therapeutic targeting in various types of cancer. Several studies have demonstrated the importance of microRNAs in cancer-related processes, such as proliferation, invasion, differentiation, metastasis, angiogenesis, apoptosis, and drug resistance (7).

In the literature, microRNAs 126 and 214 are described as serum biomarkers of neoplasia in dogs (8). Other studies also evaluated the expression of microRNAs 126 and 214 in different canine neoplasms, but using neoplastic tissues: expression in samples of healthy spleen and splenic hemangiosarcoma (9), expression in samples of canine intestine in FFPE (formalin-fixed-paraffin-embedded) material from healthy intestine and with inflammation (10).

The MDR1 gene is important in drug resistance, and microRNAs 126 and 214 are involved in mechanisms linked to cancer. Few studies in the literature simultaneously evaluated the MDR1 gene and microRNAs 126 and 214 in dogs with TVT using tumor tissue. Therefore, this study aims to evaluate in situ the expression profile of the resistance gene and microRNAs in tissue samples from dogs with TVT and tissue samples from healthy dogs.

Materials and Methods

Ethical Aspects

The study was approved by the Animal Use Ethics Committee (CEUA) of the Federal Rural University of the Amazon (UFRA) under number (9295190423/2023/CEUA/UFRA).

Samples

Eighteen mixed breed domestic dogs, male and female, aged 1 to 7 years, participated in the study. These animals were divided into two groups: the test group consisting of 9 animals affected by TVT and the control group consisting of 9 animals not affected by TVT. Samples from the test group were collected at the following locations: shelters in the municipality of Benevides, Belém, in the Outeiro neighborhood, and at the homes of dogs cared for in the "Aumigos" project of the Marituba City Hall. Samples from the control group were collected from dogs undergoing elective castration at the Zoonosis Control Center affiliated with the Belém City Hall.

The test group included animals with tumors or ulcerated lesions in the genital region (vulva, vagina, prepuce, or glans penis) and a history of free roaming. The control group included dogs without symptoms of TVT and who underwent elective castration surgery.

Samples from 9 dogs in the test group were obtained through incisional biopsy of the tumor area, after local anesthesia with 2% lidocaine hydrochloride. To obtain biological material from the control group (9 dogs), skin samples were collected from the prescrotal region of males during the castration procedure and abdominal skin from females. The tissue fragments from the test and control groups were placed in a vial containing RNAlater™ stabilization solution (Invitrogen, Carlsbad, CA, USA) and then stored in an ultrafreezer at -80ºC for laboratory procedures of analysis and expression of the MDR1 gene and microRNAs 126 and 214 at the Serology and Molecular Biology Laboratory of the Federal Rural University of the Amazon-UFRA.

Cytological Procedure

TVT samples can be classified according to their morphological pattern, determined through cytomorphological diagnosis. We follow the classification proposed by (11)**,** which subdivides TVT cells into three types: plasmacytoid, where more than 60% of cells are ovoid in shape, with abundant cytoplasm, eccentric nucleus, and abundant intracytoplasmic vacuoles; lymphocytoid, where more than 60% of cells are rounded in shape, with scarce and granular cytoplasm, central nucleus, and few intracytoplasmic vacuoles; mixed: presents both lymphocytoid and plasmacytoid types, with neither exceeding 59%.

Tumor tissue samples from dogs suspected of having TVT were confirmed through cytological examination. The collected samples were prepared using the impression method (impression of the lesion onto a glass slide). After drying at room temperature, the slides were immersed in methyl alcohol to fix the cells until staining was complete. At the Veterinary Pathology Laboratory of UFRA, the slides were stained with Romanowsky stain (Panotic Rapid®) according to the manufacturer's instructions. Subsequently, the samples were analyzed by optical microscopy to classify the type of TVT (plasmacytoid, lymphocytoid, or mixed) using an OLYMPUS CX40 microscope with 10x, 20x, and 40x objectives.

RNA Extraction

To obtain RNA, 18 tissue samples, nine from dogs with TVT and nine from dogs without TVT were extracted using

the Trizol® method (Invitrogen, Carlsbad, CA, USA) and processed according to the manufacturer's recommendations. The quantification of the total RNA samples obtained was analyzed using the NanoDrop ND-1000 equipment (Agilent, Santa Clara, CA, USA). RNA purity was determined by the A260/A280 ratios. The RNA samples from the test group were diluted to a concentration of 50ng/µL and those from the control group to a concentration of 40ng/µL.

Gene and microRNA expression (qRT-PCR)

The samples were amplified by qRT-PCR using the following genes: MDR1 and the endogenous GAPDH, microRNAs 126 and 214, and the endogenous Let-7c. The genes were designed using the online Primer3 software based on the reference sequences deposited in GenBank (Table 1) and the microRNAs were designed using the miRprimer2 software based on the reference sequences deposited in Mirbase (Table 2).

The qRT-PCR reactions were performed in two replicates at a final volume of 10 µL, using 5 µL of Sybr® Green 2x master mix (Cellco Biotec do Brasil LTDA, São Carlos, São Paulo, Brazil), 1 µL of extracted RNA (approximately 50ng/µL) for the test group samples, and 0.5µL of extracted RNA (approximately 40ng/µL) for the control group samples, 0.5 µL of each primer and 0.02 µL of reverse transcriptase SCRIPT 3.0, 40.000 U (Cellco Biotec do Brasil LTDA, São Carlos, São Paulo, Brazil), DEPC ultrapure water (Uniscience, Osasco, São Paulo, Brazil) was added until reaching the final reaction volume.

The reactions were performed using the CFX96 TouchTM Real-Time Detection System (Bio-Rad, Hercules, CA, USA) at the Serology and Molecular Biology Laboratory of UFRA, under the following conditions: step 1: 48ºC for 30 minutes, step 2: 95ºC for 2 minutes, step 3: 95ºC for 15 seconds, step 4: 60ºC for 1 minute and plateau phase, step 5: go to 3, 39 repetitions, step 6: Melt curve 65ºC to 95ºC and plateau phase: 0.5ºC for 5 seconds.

Relative gene expression was determined by the 2-(ΔCt) method, using GAPDH as the reference gene and Let-7c as the reference microRNA. In the equation, ΔCt corresponds to the difference between the Ct of the target gene and the Ct of the endogenous gene (12).

Statistical Analysis

The Shapiro-Wilk test was applied to assess data normality. Student's t-test was used to assess the relationship between the expression of the MDR1 gene and microRNAs 126 and 214 in animals with and without TVT. The significance level was set at less than 0.05. All analyses were performed using SAS (Free Version University Edition).

Table 1: Primer sequences of the MDR1 gene and endogenous GAPDH used in gene expression analysis in dogs with transmissible venereal tumors

Genes	Primers (5’ -3’)	Chromosome	ID GenBank
MDR1	F: CAGTGGTTCAGGTGGCCCT	14	403879
	R: CGAACTGTAGACAAACGATGAGCT		
GAPDH	F: GGGCCAAGAGGGTCATCATC	27	403755
	R: GATGCCGAAGTGGTCATGGA		

F: Forward; R: Reverse.

Table 2: Sequences of mature microRNAs 126, 214, and Let-7c (active forms of microRNAs) with their respective primer pairs

	Mature microRNAs	Primers (5’ -3’)
MicroRNA-126	CAUUAUUACUUUUGGUACGCG	F: CGCAGCATTATTACTTTTGGT
		R: CCAGTTTTTTTTTTTTTTTCGCGT
MicroRNA-214	ACAGCAGGCACAGACAGGCAGU	F: ACAGCAGGCACAGACA
		R:CAGGTCCAGTTTTTTTTTTTTTTTACT
Let-7c	UGAGGUAGUAGGUUGUAUGGUU	F: GCAGTGAGGTAGTAGGTTGT
		R:GGTCCAGTTTTTTTTTTTTTTTAACCA

F: Forward; R: Reverse.

Results

Study animals

The samples collected from the 18 animals in the test and control groups are detailed in Table 3, which shows the sex, breed, and age of the participating dogs. There was no variation in breed between the two groups, as all dogs were mixed breed. Regarding sex, females were more frequent in both groups. Regarding age, all animals in the control group were juvenile dogs with a minimum age of 1 year and a maximum age of 14 months, while in the test group, most dogs were mature adults aged 5 years or less. We used the age classification proposed b**y** (13).

Table 3: Classification of the variables sex, breed, and age of the dogs in the test group and dogs in the control group

Dogs with TVT		Dogs without TVT	
Sex	8 females and 1 male	Sex	8 females and 1 male
Breed	All the animals were mixed breed	Breed	All the animals were mixed breed
Age	Six were mature adult dogs (5 years or younger) and three were senior dogs (7 years).	Age	They were all juvenile dogs: seven dogs were 1 year old and two dogs were 14 months old

Macroscopic examination

Of the biopsy samples collected from 9 canines with genital lesions of TVT, in three animals the lesions were multilobular with a rough appearance as shown in figure 1A and in six of them a smooth appearance and shiny surface as illustrated in figure 1B.

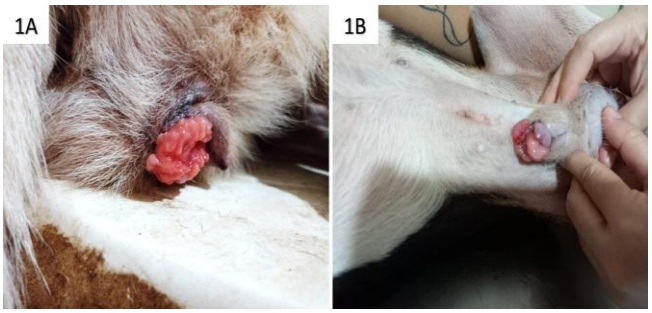

Figure 1: A) Macroscopic aspects of the neoplasm showing a rough surface, multilobulated appearance, and reddish coloration. B) Macroscopic aspects of the neoplasm showing a shiny surface, smooth appearance, and pink coloration.

Cytological Analysis

Imprint cytology was performed on the 9 dogs prior to TVT biopsy. The steps of the cytological procedure are shown in Figures 2A and 2B. In Figure 2A, the glass slide is shown being pressed onto the vulva affected by TVT (imprint method); after drying at room temperature, the slide is immersed in methyl alcohol to fix the material. Figure 2B illustrates the sequence of Romanowsky stains used to stain the slides in the Veterinary Pathology Laboratory at UFRA.

After staining, the slides were submitted to cytological diagnosis based on the cytomorphological classification proposed by (11), identifying one lymphocytoid sample, two plasmacytoid samples, and six mixed samples. Figure 3 illustrates the plasmacytoid and lymphocytoid types and the intracytoplasmic vacuoles present in TVT cells.

MDR1 Gene

The relative gene expression of MDR1 in the test group of dogs, which are the animals with canine TVT, was 10 times higher compared to the control group of animals with a significant difference observed ($P<0.05$) between the two groups as shown in Figure 4.

Figure 2: A) Female dog with TVT undergoing imprint cytology; note that the glass slide is being pressed against the vulva affected by the neoplasm. B) Romanowsky staining sequence and order of use for staining cytological slides.

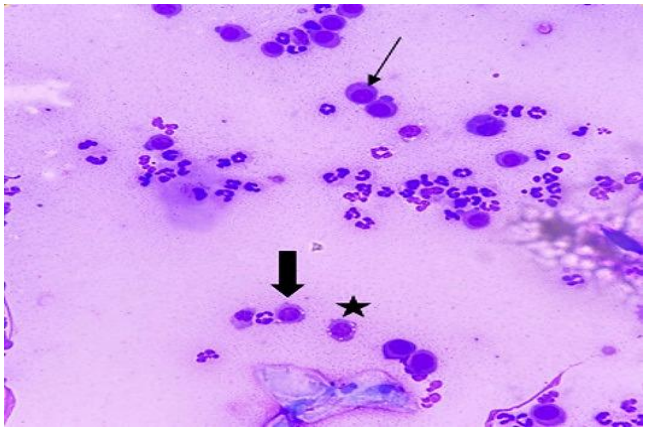

Figure 3: Cytological impression, observed by optical microscopy (40x), showing a plasmacytoid pattern of TVT (thin arrow) characterized by cells with ovoid morphology, abundant cytoplasm, and eccentric nucleus; a lymphocytoid pattern (thick arrow) characterized by cells with rounded morphology, scarce and granular cytoplasm, and central nucleus. Intracytoplasmic vacuoles of TVT cells (asterisk) are observed in both lymphocytoid and plasmacytoid types, with greater abundance in the plasmacytoid type. Rapid panoptic staining.

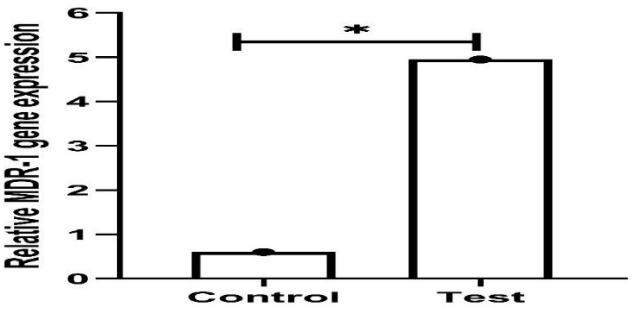

Figure 4: Relative gene expression of MDR1 mRNA obtained from neoplastic samples of canine TVT and samples from dogs without the tumor; MDR1 expression was 10 times higher in the test group, a significant difference was observed between the two groups (P<0.05)

MicroRNAs 126 and 214

Among the 18 samples used in the study, only 6 samples from the test group and 3 samples from the control group showed amplification of their gene expression. MicroRNA-126 expression showed practically basal values in dogs with TVT, and the control group samples showed expression close to 2. However, the difference between the groups was not considered statistically significant (P>0.05), as shown in Figure 5. On the other hand, a fivefold higher relative gene expression of microRNA-214 in the control group compared to the test group samples. These samples showed a significant difference (P<0.05), as shown in Figure 5.

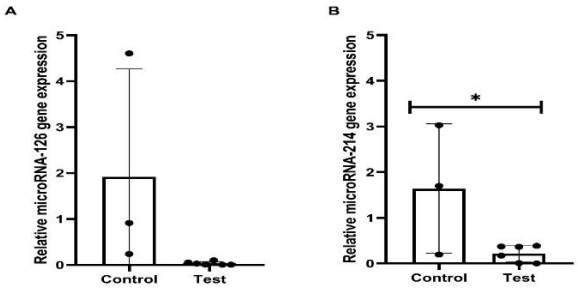

Figure 5: Relative gene expression of microRNAs 126 and 214 in samples from dogs with canine transmissible venereal tumor and dogs without the tumor. No significant differences were observed in microRNA-126 expression between the two groups. A significant difference was observed between the two groups (P<0.05) in relation to microRNA-214, which showed baseline values in the test group.

Discussion

Our results indicate that in the test group (dogs with TVT), all were mixed breed, mostly female dogs, and mature adults (5 years or younger). These data corroborate the study by (14), a literature review focused on epidemiological aspects of 3,622 cases of TVT in Brazil between 2000 and 2020, which observed that the dogs most affected by TVT were mixed breed, female, and adults (between 2 and 7 years old). In relation to the control group (dogs without TVT), all dogs were mixed breed, mostly female dogs, and juveniles aged 1 year. Therefore, the differences observed between the two groups in our study were related to age range.

Our study evaluated the expression of the multidrug resistance gene, called MDR1 or ABCB1, which encodes cellular P-glycoprotein (p-gp) (15). P-gp's mechanism of action involves using energy from ATP hydrolysis to transport drugs, toxins, xenobiotics, and other macromolecules to the extracellular environment against the concentration gradient (15).

P-gp is predominantly expressed in regions that function as epithelial barriers or play an excretory role, such as the gastrointestinal tract, blood-tissue barrier, liver, and kidneys. This indicates that MDR1 may play a key role in carcinogen elimination, and its mutation may be associated with the development of malignant tumors in humans (16).

We identified high expression of the MDR1 gene in adult dogs with TVT, compared to the decreased expression identified in juvenile dogs without TVT. The MDR1 gene is expressed in canine tumor tissues, and its expression may be associated with resistance in tumors (17). The published review (18) points to several studies in which MDR1 expression is observed in neoplastic cell lines from dogs with different types of neoplasms: lymphoid leukemia, osteosarcoma, mast cell tumor, adrenal carcinoma, liver carcinoma, mammary carcinoma, lung carcinoma, gastrointestinal carcinoma, transitional cell carcinoma, malignant lymphoma and mast cell tumor. The literature shows that MDR1 is expressed in dogs with and without neoplasms and is associated with drug resistance in canine cancer; however, age is not identified as a determining factor influencing the expression of this gene.

We used quantitative real-time PCR (qRT-PCR) to evaluate MDR1 gene expression in tissue samples from dogs with canine transmissible venereal tumors and abdominal and prescrotal skin samples from healthy dogs. Other studies have also used the same technique to evaluate MDR1 gene expression in canine neoplasms (4-6).

Our finding regarding low MDR1 gene expression in skin biopsies from clinically healthy dogs differs from (5), which identified high MDR1 gene expression in normal liver samples from clinically healthy dogs. This discrepancy is possibly due to the type of tissue used, as our study used skin samples, unlike the study (5), which used normal liver samples. In human literature, studies have shown that the MDR1 gene is expressed in several organs including kidneys, rectum, colon, liver, lungs and adrenal gland, in contrast, lower expression of the gene is observed in the prostate, brain, heart, skin, stomach and esophagus (19).

Our study differs from findings in the literature (5) because, while we identified increased expression of the MDR1 gene in dogs with TVT, the authors observed reduced expression of the same gene in dogs with lymphoma. The observed difference may be due to some factors such as DNA mutations, chemical changes in histone proteins and DNA that lead to epigenetic alterations, changes in chromatin structure, and many other processes that modify gene expression in cancer (20).

We identified increased MDR1 gene expression in tumor samples from dogs with TVT prior to the start of chemotherapy treatment corroborate the findings of (4), who evaluated MDR1 gene expression before and during chemotherapy in dogs with malignant lymphoma. They identified high gene expression before treatment in the group of dogs that tolerated chemotherapy well, and in this group, 18 polymorphisms were found.

The literature mentioned that polymorphisms in the promoter region are indicated to alter the transcription levels of the MDR1 gene (21,22). The increased MDR1 gene expression that we identified in our study could be explained by the presence of polymorphisms in the TVT samples, however, we did not perform the evaluation of polymorphisms and we did not evaluate MDR1 gene expression in dogs during chemotherapy. The literature mentioned a pioneering study in which a higher expression of MDR1 was observed in TVT cells in vitro after treatment with vincristine (6).

The high expression of MDR1 that we identified in dogs with TVT demonstrates that this gene is expressed in this type of neoplasm. Upregulation of P-gp expression has been associated with several factors, such as cancer-specific genomic instability and the presence of inflammatory stressors and epigenetic mechanisms in the tumor microenvironment. Research indicates that genetic rearrangements and tumor mutational burden play an essential role in the control and modulation of the MDR1 gene promoter region, resulting in its expression (23).

We emphasize that further studies should be conducted to evaluate the multidrug resistance gene in dogs from different locations in the Belém metropolitan region to identify possible regional variations. Limitations of this study include the small number of samples, only nine tissue samples were from dogs with TVT and nine were skin biopsies from clinically healthy dogs, which limits the generalizability of the findings, the lack of assessment of MDR1 gene expression during and after chemotherapy treatment, and the fact that only tumor tissue samples were used in the gene expression analysis. Other biological samples, such as blood and TVT cell cultures, could have been used in the sample composition.

MicroRNAs play a fundamental role in biological activities, controlling gene expression after transcription. They act as tumor suppressor genes when involved in tumor formation and progression, and as oncogenes when they act to block the cell cycle (24). In dogs, microRNAs 214 and 126 participate in the regulation of several mechanisms such as angiogenesis, proliferation, migration, and cell death of tumor cells, with tumor progression being affected by the dysregulation of these two microRNAs (8).

MicroRNAs can be measured in samples from all tissues and fluids, such as blood, plasma, serum, urine, semen, saliva, pleural fluid, and ascites (25). When present in blood samples, they circulate in the bloodstream after being released by cells or during apoptosis. Once in the bloodstream, they are stabilized by binding to proteins or being enveloped by exosomes and microvesicles (10).

This study is pioneering in evaluating the expression of microRNAs in dogs with TVT using tumor samples. Our findings demonstrate reduced expression of microRNA-214 in samples of cells with genital tumors, different from the result observed in the literature where blood samples from dogs with genital tumors were used and a moderate increase in microRNA-214 was identified, but without a significant difference (7). Therefore, the discrepancy observed in the expression of microRNA-214 in our study and the literature (7) may be due to differences in gene expression profiles that are modulated according to the tissue, cell type, treatment, or disease (26).

Other studies corroborate our finding of reduced microRNA-214 expression in tumor samples, negative microRNA-214 expression in spleen samples from splenic hemangiosarcoma (9), and identification of reduced microRNA-214 expression in small bowel T-cell lymphomas and large bowel B-cell lymphomas using intestinal samples preserved in formalin-fixed paraffin-embedded (FFPE) material (10). The concordance observed between our study and the literature (8,9) can be explained by the downregulation of microRNA-214. Some microRNAs are upregulated and others are downregulated in cancer (27).

Tumor suppressor genes are downregulated in neoplasms; they play a role in tumorigenesis and in the development and cure of cancer (24). Our results suggest that microRNA-214 acts as a tumor suppressor gene in TVT cells, due to its low expression behavior in animals that present the neoplasia.

As we age, cells undergo several modifications, such as: DNA damage, including chromosomal aneuploidies, mitochondrial DNA mutations and telomere loss, as well as epigenetic changes, which represent mechanisms related to aging (28). Three main mechanisms mediate epigenetic modifications: DNA methylation, histone modification, and regulatory microRNAs (29).

We identified differences in the expression of microRNA-214, which was increased in the group without TVT (transmissible venereal tumor) composed of juvenile dogs, and decreased in the group of dogs with TVT, which

were mostly adults. Age may be a determining factor in microRNA expression, as shown in the study by (30), which evaluated microRNA expression in the ovaries, oviducts, and uteruses of young, old, and uteropathic bitches, and demonstrated high expression of microRNAs 708, 151, 140, 30d, among others, in older bitches. Although the study by (30) did not measure microRNA-214, the object of our study, the results show that individual microRNAs vary according to age in dogs.

We acknowledge that the main limitations of this study in analyzing microRNA expression were the number of samples used, which limits the generalizability of the results and the lack of another sample source, such as circulating blood, for possible comparisons. Future perspectives include the need for more studies on microRNA expression in dogs with TVT, as they are rare. Furthermore, we suggest the possible use of microRNA-214 as a prognostic marker in dogs with TVT, requiring further research to use a larger sample size and different types of biological samples.

Conclusion

High expression of the MDR1 gene is observed in dogs, regardless of the cytological type of TVT; however, further studies with chemotherapy treatment are needed. The low expression of microRNA-214 in tumor samples indicates a potential role as a tumor suppressor in this type of neoplasia. Future studies should evaluate these markers during and after treatment, in samples from different origins and regions, to confirm their prognostic and therapeutic value.

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Conflict of interest

The authors of this manuscript declare that there is no conflict of interest regarding the writing process or data analysis.

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التعبير عن الجين المقاوم للأدوية المتعددة والـ microRNAs في الأورام التناسلية الزهرية في الكلاب

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الخلاصة

الصدمة النزفية هي السبب الرئيسي في معدل الاصابة ومعدل النفوق وكثيرا ما خلل متعدد الأعضاء، وخاصة ضرر الكلى الحاد. ومع ذلك، فإن نوع السائل الأمثل لاستعادة استقرار الدورة الدموية مع حماية الأعضاء لا يزال غير مؤكد. قارنت هذه الدراسة الإنعاش باستخدام محلول لاكتات مقابل الإنعاش البلوري الغرواني المشترك (محلول لاكتات مع الجيلاتين) من حيث معالجة الاعضاء والغير النسجي الكلوي بعد صدمة النزف في نموذج الأرنب. تم تقسيم الأرانب لأربع مجموعات: السيطرة السلبية (بدون صدمة نزفية وبدون إنعاش)، السيطرة الإيجابية (صدمة نزفية وبدون إنعاش)، مجموعة معاملة ١ (صدمة نزفية مع انعاش بمحلول لاكتات)، و مجموعة معاملة ٢ (صدمة نزفية مع انعاش بمحلول لاكتات مع الجلاتين). تم تحفيز النهاب الغدد العرقية المقيح عن طريق سحب ٣٥ ٪ من حجم الدم المقدر. تم قياس وظائف الكلى من مرحلة ما قبل النزفية (الوقت ١٥) مرحلة ما بعد الإنعاش (الوقت ٢٣٠)، تبعها أمراض الأنسجة الكلوية ودرجات الضرر. في مجموعة السيطرة الايجابية حصل فقدان وظيفة شديد للاعضاء، مع ضرر نسيجي كلوي هائل (الدرجة ٤). في كل من استراتيجيات الإنعاش استقرت وظيفة الكلى؛ ومع ذلك، كانت أدنى درجة إصابة ١,٥ في مجموعة المعاملة ٢ مقارنة مع مجموعة المعاملة ١. أظهرت مجموعة السيطرة الايجابية زيادة كبيرة في الكرياتينين (١٦٧,٦٢±٤٢,٩٩، إ=٠,٠١٣) و نيتروجين اليوريا في الدم (١٣,٠٦±٤,٨٧، إ=٠,٠٣١) عند الوقت ٢٣٠، مما يشير إلى ضعف كلوي حاد. في المقابل، حافظت مجموعة المعاملة ٢ (لاكتات مع الجيلاتين) على وظيفة الكلى مستقرة (الكرياتينين: ١١٠,١٢، إ=٠,٥٦٤ ؛ نيتروجين اليوريا في الدم: ٩,٣٠، إ=٠,٣٩٨). على الرغم من أن جميع مجموعات الصدمة النزفية أظهرت تخفيفا كبيرا للدم (كريات الدم الحمر: ٣,٥١±٠,٥٠، إ=٠,٠٠٢؛ الهيموكلوبين: ٦,٠٠±١,١٠، إ=٠,٠٠١، الهيماتوكرت: ٢٣,٧٥±٣,٥٠، إ=٠,٠٠١. مجموعة المعاملة ١ ومجموعة المعاملة ٢ كانت فعالة في منع ضرر الكلى الحاد واستقرار وظيفة الكلى. في الاستنتاجات، تقدم هذه الدراسة أدلة جديدة على أن الجمع بين اللاكتات والجيلاتين يوفر حماية متميزة لهيكلية الكلى بعد صدمة النزف.

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