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ВЛИЯНИЕ НАНОЧАСТИЦ СЕРЕБРА НА АНТИБИОТИКОРЕЗИСТЕНТНОСТЬ МИКРООРГАНИЗМОВ ПРИ ЛЕЧЕНИИ ЭНДОМЕТРИТА КОРОВ

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Главный этиологический фактор возникновения эндометритов – патогенная и условно-патогенная микрофлора, проникающая в матку в послеродовой период, во время течки, искусственного осеменения загрязненной спермой. Проведено исследование с целью изучения изменения антибактериальной чувствительности микроорганизмов при терапии послеродового гнойно-катарального эндометрита коров препаратом, содержащим наночастицы серебра. Для изучения роли условно-патогенной микрофлоры в этиологии послеродовых гнойно-катаральных эндометритов проведено клиническое исследование 150 коров в условиях хозяйства Новосибирской области в период массового отела. Животных по принципу аналогов разделили на опытную и контрольную группы. Контрольной группе вводили рыбий жир внутриматочно в дозе 150 мл с окситетрациклином гидрохлоридом в дозе 40 мг/кг живой массы, 1 раз в 48 ч и утеротон внутримышечно в дозе 10 мл, однократно 1 раз в 48 ч. Опытной группе вводили внутриматочно 10%-й водный раствор арговита в дозе 100 мл, 1 раз в 48 ч и утеротон внутримышечно 10 мл, однократно 1 раз в 48 ч. Установлено, что при лечении послеродового гнойно-катарального эндометрита коров препаратом арговит уменьшается средний срок лечения заболевания в 1,8 раза по сравнению препаратом в контрольной группе. При лечении послеродового гнойно-катарального эндометрита коров препаратом арговит установлен рост антибиотикочувствительности изолированной микрофлоры к 21 препарату (87,5%) – от 1,2 до 100%. В контрольной группе отмечено снижение антибиотикочувствительности выделенной микрофлоры к 18 (75%) препаратам – от 1,1 до 28,7%.

Ключевые слова: гнойно-катаральный эндометрит, наночастицы серебра, антибиотикорезистентность, микроорганизмы

EFFECT OF SILVER NANOPARTICLES ON ANTIBIOTIC RESISTANCE OF MICROORGANISMS IN THE TREATMENT OF ENDOMETRITIS IN COWS

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The main etiological factor in endometritis is pathogenic and opportunistic pathogenic microflora entering the uterus during the postpartum period, during estrus, artificial insemination with contaminated sperm. A study was carried out to investigate changes in antibacterial sensitivity of microorganisms during therapy after labor purulent-catarrhal endometritis of cows with a preparation containing silver nanoparticles. To study the role of opportunistic pathogenic microflora in the etiology of postpartum purulent-catarrhal endometritis a clinical study of 150 cows in a farm in the Novosibirsk region during mass calving was carried out. Animals were divided into experimental and control groups according to the analogy principle. The control group received fish oil intramuscularly in a dose of 150 ml with oxytetracycline hydrochloride in a dose of 40 mg/kg of live weight once every 48 hours and uteroton intramuscularly in a dose of 10 ml once every 48 hours. The experimental group received intrauterine injections of argovit 10% aqueous solution at a dose of 100 ml once every 48 h and uteroton intramuscularly at a dose of 10 ml once every 48 h. It was found that the treatment of postpartum purulent-catarrhal endometritis of cows with argovit decreased the average duration of treatment of the disease by 1.8 times compared to the preparation in the control group. When treating postpartum purulent-catarrhal endometritis of cows with argovit, an increase in antibiotic sensitivity of the isolated microflora to 21 drugs (87.5%) from 1.2 to 100% was found. In the control group, there was a decrease in antibiotic sensitivity of the isolated microflora to 18 (75%) preparations from - 1.1 to 28.7%.

Keywords: clinical endometritis, silver nanoparticles, antibiotic resistance, microorganisms.

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INTRODUCTION

The increase in the reproduction of herds is greatly slowed down by the spread of the breeding stock infertility, which is caused by gynecological pathologies. Inflammatory processes in the uterus take a chronic course due to untimely treatment of acute endometritis, as well as incomplete course of therapy. Endometritis, which reduces milk productivity, reproductive ability, and milk quality, leading to premature culling and failure to produce animal yield, is one of the most common gynecological diseases of cattle [1-5].

Endometritis of bacterial origin remains one of the most pressing problems of veterinary medicine. Due to the complexity of the etiology of this disease, it is currently impossible to develop a specific prevention and therapy, which entails uncontrolled use of broad-spectrum drugs. Their long-term uncontrolled use has led to global antibiotic resistance of microorganisms [6, 7]. This raises the need for the latest complex drugs. One of the promising areas of modern pharmacology is the creation of new drugs using nanotechnology products, which opens up the possibility of increasing their effectiveness [8, 9].

The purpose of the study was to investigate the change in antibacterial sensitivity of microorganisms during the therapy of postpartum purulent-catarrhal endometritis of cows with a preparation containing silver nanoparticles.

MATERIAL AND METHODS

To study the role of opportunistic microflora in the etiology of postpartum purulent-catarrhal endometritis a clinical study of 150 cows under farm conditions in the Novosibirsk region was carried out. Endometritis diagnostics, treatment, typing and antibiotic sensitivity determination of the isolated microorganisms were carried out according to the "Methodical instructions on diagnostics, therapy and prophylaxis of reproductive organs diseases of cows and heifers" (2005). The material for examination was vaginal mucus secretion before and after treatment. The vaginal secretion was collected with a sterile cotton-gauze tampon after a thorough cleaning of the vulva and the root of the tail with a tampon moistened with 70% ethyl alcohol rectifying agent.

Bacteriological examination was performed by inoculating the vaginal mucus secretion on 5% blood agar, MPA with 1% glucose, and Endo medium. Staphylococci and streptococci were isolated using a selective supplement ("StaphStrepto Supplement", India). Identification of microflora isolated from sick cows was carried out taking into account cultural, morphological and biochemical properties of bacteria according to generally accepted methods (Bergey's Bacterial Identifier, 2000). Biochemical properties of bacteria were studied using a set of reagents - biochemical plates differentiating enterobacteriaceae (SPA Diagnostic Systems LLC, Nizhny Novgorod), streptococci

(Strepto-test 16 Erba Lachema s.r.o., the Czech Republic), staphylococci (Staphytest- 24 Erba Lachema s.r.o., the Czech Republic).

Microflora sensitivity was investigated by disco-diffusion method on Mueller-Hinton agar (Bio-Rad, USA) in accordance with the criteria of the European Committee for Antibiotic Susceptibility Testing (EUCAST, 2018). Multiple drug resistance was defined as resistance to three or more antibacterial agents.

Argovit drug is a complex of highly dispersed nanoparticles of cluster silver, polyvinylpyrrolidone and aqueous solution obtained by electrobeam method. It has a wide range of antimicrobial action against Gram-positive and Gram-negative, aerobic and anaerobic, spore-forming and asporogenic bacteria in the form of monocultures and microbial associations.

Fish oil (veterinary fat), derived from fish and marine mammals, is a source of vitamins and polyunsaturated fatty acids, 1 ml of which contains vitamins: E - 600 micrograms, A - 500 IU and D3 - 30 IU. It is used internally for prevention and treatment of vitamin A deficiency, rickets, chronic infections, sexual disorders in animals.

Oxytetracycline hydrochloride is an antibacterial drug of the tetracycline group that is effective against rickettsiae, gram-negative and gram-positive microbes.

Uterotone has a blocking effect on myometrial beta-adrenoreceptors, which contributes to the activity of endogenous oxytocin, resulting in increased uterine smooth muscle contractions.

Animals were divided into experimental and control groups according to the analogy principle. The control group (n = 75) received fish oil intrauterinely in a dose of 150 ml with oxytetracycline hydrochloride in a dose of 40 mg/kg live weight once every 48 hours and Uteroton intramuscularly in a dose of 10 ml, once every 48 hours. The experimental group received intrauterine injections of Argovit 10% aqueous solution in a dose of 100 ml once every 48 hours and Uteroton intramuscularly in a dose of 10 ml once every 48 hours.

RESULTS AND DISCUSSION

Microbiological studies of mucus from the cervical-vaginal canal of cows with postpartum endometritis revealed microorganisms of *Streptococcus* spp. in 24.1% of samples, *Staphylococcus* spp. - 22.5, *E. coli* 20.0, *S. enteritidis* 19.2, and *Pr. vulgaris* 14.2% of samples, respectively (see Table 1). Bacteriological studies of uterine and vaginal secretions of cows with postpartum purulent-catarrhal endometritis revealed the following associations of microorganisms: *Str. pyogenes* + *St. aureus* + *Pr. vulgaris* + *E. coli* (47.5%), *Str. pyogenes* + *E. coli* (19.2), *S. enteritidis* + *E. coli* + *Pr. vulgaris* (15.8), *St. aureus* + *E. coli* (10) and *Str. pyogenes* + *St. aureus* (7.5%).

Laboratory studies of microbial isolates showed high sensitivity to oxytetracycline, which justified its use as a control drug in the production trial of Argovit. The results of the study revealed significant therapeutic efficacy in the treatment of postpartum purulent catarrhal endometritis in cattle with silver-containing drug Argovit compared with an antibacterial agent. During therapy with Argovit the average period of treatment of cows was 7,8 ± 0,1 days,

Табл. 1. Микроорганизмы, выделенные из маточно-влагалищных выделений коров, больных послеродовым гнойно-катаральным эндометритом

Table 1. Microorganisms isolated from the uterine-vaginal secretions of cows with postpartum purulent-catarrhal endometritis

Microorganism	Number of isolates	%
Streptococcus pyogenes	29	24,1
Streptococcus aureus	27	22,5
Escherichia coli	24	20,0
Salmonella enteritidis	23	19,2
Proteus vulgaris	17	14,2
Str. pyogenes + *St. aureus* + *Pr. vulgaris* + *E. coli*	57	47,5
Str. pyogenes + *E. coli*	23	19,2
Salmonella + *E. coli* + *Pr. vulgaris*	19	15,8
St. aureus + *E. coli*	12	10,0
Str. pyogenes + *St. aureus*	9	7,5

which is 1,8 times shorter in comparison with the complex preparation (fish oil + oxytetracycline hydrochloride) in the control group, where the period of treatment was 14,1 ± 0,6 days.

After treatment of cows with postpartum purulent-catarrhal endometritis, the control group showed a decrease in antibiotic sensitivity of the isolated microflora to 18 (75%) drugs, from 1.1 to 28.7%. A slight increase to tylosin, lincomycin, polymyxin, erythromycin, gentamicin and carbenicillin was detected, from 3.7 to 24.8%. When cows were treated with Argovit, there was an increase in antibiotic sensitivity of isolated microflora to 21 drugs (87.5%), from 1.2 to 100%, with simultaneous decrease of sensitivity to doxycycline, enrofloxacin and oxytetracycline from 3.1 to 23.2% (see Table 2).

The obtained results of enhancing the bactericidal effect when AgNPs are used together with antibacterial drugs are confirmed in other studies as well. S. Z. Naqvi et al. [10] described the combined effect of concomitant use of antibacterial drugs and silver nanoparticles against multidrug-resistant bacteria. It was found that the synergistic effect of antibiotics (ciprofloxacin, imipenem, gentamicin, vancomycin, trimethoprim) and nanoparticles led to an increase in antibacterial activity by 0.2-7.0 (average 2.8) times. This confirms that nanoparticles can be effectively used in combination with antibiotics to increase their effectiveness against various pathogenic microbes. M.S.M. Mohamed et al. [11] described the antibacterial effect of combined use of AgNPs and vancomycin against *St.*

Табл. 2. Изменение уровня чувствительности выделенной микрофлоры к антибиотикам при лечении гнойно-катарального эндометрита (*n* = 40), %

Table 2. Change in the level of sensitivity of the isolated microflora to antibiotics in the treatment of purulent-catarrhal endometritis (*n* = 40), %

Antibiotic	Control group, *n* = 40		%	Experimental group		%
	Before treatment	After treatment		Before treatment	After treatment	
Amoxicillin	12,9 ± 0,9	11,3 ± 0,5	–12,4	15,2 ± 0,3	18,7 ± 0,1	+23
Ampicillin	15,3 ± 0,1	10,9 ± 0,4	–28,7	16,2 ± 0,5	17,1 ± 0,4	+5,5
Amikacin	14,3 ± 1,0	12,8 ± 0,2	–10,4	16,5 ± 0,2	16,7 ± 0,7	+1,2
Benzyl-penicillin	16,1 ± 0,3	15,3 ± 0,1	–4,9	16,1 ± 0,1	16,7 ± 0,4	+3,1
Gentamicin	15,3 ± 0,8	17,4 ± 0,2	+13,7	18,9 ± 0,4	21,4 ± 0,1	+13,2
Doxycycline	16,1 ± 0,1	14,3 ± 0,9	–11,2	16,3 ± 0,1	15,8 ± 0,5	–3,1
Carbenecillin	12,5 ± 0,7	15,6 ± 0,2	+24,8	20,1 ± 0,4	21,8 ± 0,4	+8,4
Norfloxacin	16,2 ± 1,1	12,3 ± 0,9	–24,1	16,3 ± 0,7	17,4 ± 0,1	+6,7
Neomycine	13,7 ± 0,5	12,6 ± 0,3	–8	16,9 ± 0,5	18,5 ± 0,2	+9,5
Polymyxin	12,1 ± 0,7	13,1 ± 0,4	+8,3	16,4 ± 0,7	17,5 ± 0,3	+6,7
Rifampicine	15,2 ± 0,2	14,1 ± 0,1	–7,2	–	15,6 ± 0,1	+100
Streptomycin	19,9 ± 0,1	15,6 ± 0,7	–21,6	17,4 ± 0,2	18,1 ± 0,1	+4
Enrofloxacin	19,3 ± 0,6	17,5 ± 0,1	–9,3	18,9 ± 0,7	16,3 ± 0,2	–13,7
Ciprofloxacin	18,1 ± 0,8	16,7 ± 0,5	–7,7	16,9 ± 0,3	19,2 ± 0,4	+13,6
Tetracyclin	18,3 ± 0,4	17,1 ± 0,7	–6,5	–	17,1 ± 0,6	+100
Oxytetracycline	22,1 ± 0,7	17,8 ± 0,5	–19,4	23,2 ± 0,5	17,8 ± 0,7	–23,2
Ofloxacin	17,3 ± 0,5	16,2 ± 0,1	–6,3	–	18,4 ± 0,6	+100
Lincomycin	17,6 ± 0,2	18,7 ± 0,4	+6,2	16,9 ± 0,5	18,1 ± 0,3	+7,1
Tylosin	13,7 ± 0,6	14,2 ± 0,1	+3,7	17,8 ± 0,4	18,5 ± 0,1	+3,9
Tobramycin	17,3 ± 0,2	17,1 ± 0,4	–1,1	17,6 ± 0,7	18,4 ± 0,7	+4,5
Laevomycetin	17,5 ± 0,1	16,2 ± 0,3	–7,4	–	15,6 ± 0,1	+100
Ceftiofur	16,7 ± 0,3	15,8 ± 0,6	–5,4	16,1 ± 0,8	16,7 ± 0,2	+3,7
Ofloxacin	17,8 ± 0,6	16,6 ± 0,1	–6,7	16,5± 0,5	16,8 ± 0,1	+1,8
Erythromycin	14,2 ± 0,4	15,7 ± 0,8	+10,5	18,3 ± 0,4	19,1 ± 0,7	+4,4

aureus, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*.

Synergistic effect of AgNPs in combination with erythromycin and levofloxacin against *St. aureus* was noted. Antimicrobial activity with antibiotics compared to pure silver nanoparticles increased by 1.16-1.32 times. This synergism may be relevant for the treatment of infections caused by multidrug-resistant bacteria [12].

The results of the studies confirm the synergistic antibacterial effect of the combined use of AgNPs and antibacterial agents, which was established by determining the antimicrobial activity of AgNPs and chlorhexidine gluconate against the five most common pathogenic bacteria of the human oral cavity. The average MIC value of AgNPs for *Streptococcus mutans* MTCC 497 was 60 ± 22.36 µg/ml, *Str. oralis* MTCC 2696 - 45 ± 11.18, *Lactobacillus asidorhylus* MTCC 10307 - 15 ± 5.59, *L. fermentum* - 90 ± 22.36, *Candida albicans* MTCC183- 2.82 ± 0.68 µg/ml respectively. For chlorhexidine gluconate, the mean MIC of *Str. mutans* MTCC 497 was 300 ± 111.80 µg/ml, *Str. oralis* MTCC 2696 was 150 ± 55.90, *L. acidophilus* MTCC 10307 was 450 ± 111.80, *L. fermentum* was 450 ± 111.80 and *C. albicans* MTCC 183 was 150 ± 55.90 µg/ml [13].

The results of the studies showed the intensity of bactericidal properties depending on the type of the studied preparation. Literature data confirm the evaluation of the antibacterial effect of using AgNPs and antibiotics against bacteria isolated from animals that show resistance to antibiotics by serial dilution method. The minimum inhibitory concentrations of both types of antimicrobials were determined, both individually and in combination. The fractional index of inhibitory concentration was calculated and used to classify the observed collective antibacterial activity as synergistic, additive (only the sum of the individual drug effects), indifferent (no effect), or antagonistic. Of the 40 tests performed, 7 were synergistic, 17 were additive, and 16 were indifferent. None of the combinations tested showed an antagonistic effect. Most synergistic effects were observed for combinations of AgNPs administered together with gentamicin, but the greatest increase in antibacterial activity was found for combination therapy together with penicillin G against *Actinobacillus pleuropneumoniae. A. pleuropneumoniae* and *Pasteurella multocida*, initially resistant to amoxicillin, gentamicin and colistin, were sensitive to these antibiotics when combined with AgNPs. A study shows that AgNPs have potential as adjuvants for the treatment of bacterial diseases in animals [14].

The analysis of the studies allows us to identify some regularities in the changes of antibacterial properties of the preparations when they are used mono- and in combination. The presence of pronounced antibacterial properties in the Argovit preparation containing AgNPs both in monovariant use and in combination with antibacterial preparations was noted. At the same time, the inclusion of AgNPs and DMSO has a pronounced synergistic effect and significantly reduces the antibiotic concentration at which the bactericidal effect is fixed. The highest sensitivity of both AgNPs and their combinations with antibiotics was found in the reference strain *E. Coli* ATCC 25922 strain compared to the *E. coli* isolate isolated from an animal with a clinical manifestation of an infectious disease. The combination of AgNPs and the antibiotics enrofloxacin, gentamicin, ceftimag, cipromag, oxytetracycline, and ampicillin showed the greatest increase in bactericidal activity against both *E. coli* ATCC 25922 and the *E. coli* isolate than the combination of AgNPs + antibiotic + DMSO, except for cloxacillin when studied with the *E. coli* isolate [9, 15].

Increasing the effectiveness of antimicrobial activity due to combinations of AgNPs and antibiotics will allow the use of antibiotics that have fallen out of use due to bacterial resistance problems, providing additional treatment options in the health, veterinary and agricultural sectors. The studies conducted confirm the results of I.A. Mamonova[1] on the ability of metal nanoparticles to restore the sensitivity of *E. coli*

[1]Mamonova I.A. Effect of transition metal nanoparticles on antibiotic-resistant strains of microorganisms: thesis abstract of the Can. Sci. in Biology. M., 2013. 21 p.

strains to some β-lactam antibiotics (ampicillin, amoxicillin) and aminoglycosides.

The results obtained open the prospect of further studies of AgNPs to evaluate the synergistic qualities of increasing the bactericidal properties of antibiotics against a wide range of infectious pathogens in the treatment of a wide range of pathologies.

CONCLUSION

When treating postpartum purulent-catarrhal endometritis of cows with the drug argovit, an increase in antibiotic sensitivity of the isolated microflora to 21 drugs (87.5%) from 1.2 to 100% was found. After treatment with the given preparation in cows suffering from postpartum purulent-catarrhal endometritis, the control group showed the decrease of antibiosensitivity of isolated microflora to 18 (75%) preparations from 1,1 to 28,7%. At the same time a slight increase to tylosin, lincomycin, polymyxin, erythromycin, gentamicin, and carbenicillin was observed, from 3.7 to 24.8%.

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