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UNIVERSIDADE ESTADUAL PAULISTA “JÚLIO DE MESQUITA FILHO”
FACULDADE DE MEDICINA VETERINÁRIA E ZOOTECNIA
PROGRAMA DE PÓS-GRADUAÇÃO EM BIOTECNOLOGIA ANIMAL

EFEITO DA PENTOXIFILINA ORAL NA RESPOSTA
INFLAMATÓRIA E ACÚMULO DE FLUIDO INTRAUTERINOS
APÓS INSEMINAÇÃO ARTIFICIAL E TAXA DE RECUPERAÇÃO
EMBRIONÁRIA EM ÉGUAS VELHAS

ODILON MARQUEZ DE OLIVEIRA

Botucatu - SP

Maio, 2022

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RESUMO

A maioria das éguas doadoras de embrião tem a limpeza uterina prejudicada devido a problemas uterinos e cervicais como resultado de repetidas inseminações e coletas de embrião. Esses problemas levam à suscetibilidade à endometrite persistente pós cobertura (EPPC) que está associada à inflamação persistente, que mostra edema uterino excessivo, acúmulo de líquido intrauterino (FIU), grande número de neutrófilos polimorfonucleares na citologia e cultura positiva. A intensa e prolongada inflamação endometrial cria um ambiente uterino desfavorável ao desenvolvimento embrionário, resultando em queda na fertilidade. A pentoxifilina é um fármaco reolítico, que promove aumento da maleabilidade das hemácias, e apresenta efeitos anti-inflamatórios e antioxidantes. Sendo amplamente utilizado na prática clínica equina e na reprodução por aumentar o fluxo sanguíneo para os diversos tecidos. Este estudo teve como objetivo avaliar a resposta inflamatória uterina pós inseminação artificial e a recuperação embrionária de éguas doadoras velhas e subférteis tratadas com pentoxifilina. Doze éguas ($16 \pm 3,7$ anos) foram classificadas como suscetíveis ou resistentes à EPPC com base no histórico reprodutivo, nos achados ultrassonográficos e na taxa de recuperação embrionária. No início do estudo, uma amostra de biópsia foi coletada para determinar o score de biópsia do padrão Kenney e Doig. Cada égua foi submetida a seis ciclos estrais. Durante os dois primeiros ciclos, todas as éguas receberam, por via oral, 50mL de um suplemento comercial acrescido de 17mg/kg/dia de Pentoxifilina. Os dois ciclos subsequentes foram usados como washout (sem suplemento, sem pentoxifilina). Nos dois últimos ciclos, 50mL de suplemento comercial puro foi administrado por via oral. As coletas de embrião foram realizadas oito ou nove dias após ovulação. A palpação transretal e a ultrassonografia foram realizadas diariamente para avaliar o controle folicular, edema endometrial e acúmulo de fluido intrauterino. A citologia endometrial foi realizada pré e pós (24, 48 e 72h) inseminação artificial, enquanto a cultura uterina foi realizada pré e 72h pós inseminação. As contagens de neutrófilos relacionada aos efeitos do tempo não diferiram entre os grupos, bem como o edema uterino, o acúmulo de fluido intrauterino e a cultura positiva ($P > 0,05$). A recuperação embrionária foi maior no grupo pentoxifilina ($P = 0,046$). Em conclusão, a suplementação com pentoxifilina pode ser uma alternativa para diminuir a resposta inflamatória endometrial pós inseminação artificial e pode melhorar a taxa de recuperação embrionária.

Palavras-chave: Éguas, transferência de embriões, endometrite, fertilidade, pentoxifilina.

OLIVEIRA, O.M. **Effects of oral pentoxifylline on intrauterine inflammatory response and fluid accumulation after artificial insemination, and embryo recovery rate in old mares.** Botucatu, 2022. 65p. Dissertação (Mestrado) – Faculdade de Medicina Veterinária e Zootecnia, Campus de Botucatu, Universidade Estadual Paulista.

ABSTRACT

Most embryo donor mares have impaired uterine clearance due to uterine and cervical problems as a result of repeated breeding and embryo flushing. These issues lead to susceptibility to persistent breeding induced endometritis (PBIE) that is associated with persistent inflammation, which shows excessive uterine edema, intrauterine fluid accumulation, large number of polymorphonuclear cells on cytology and positive culture. Intense and prolonged endometrial inflammation creates an unfavorable uterine environment for embryonic development, resulting in a decrease in fertility. Pentoxifylline is a reolytic drug that promotes increased blood cells malleability and has anti-inflammatory and antioxidant effects. Being widely used in equine clinical practice and also in reproduction by increasing blood flow to the various tissues. This study aimed to assess the post-breeding inflammatory response and embryo recovery of sub fertile aged donor mares treated with pentoxifylline. Twelve mares (16 ± 3.7 years old) were classified as susceptible or resistant to PBIE based on the reproductive history, ultrasound findings and embryo recovery rate. At the beginning of the study a biopsy sample was taken to determine the Kenney and Doig biopsy score. Each mare was submitted to six estrous cycles. During the first two cycles, all mares received orally, 50mL of a commercial supplement added with 17mg/kg/day of Pentoxifylline. The two subsequent cycles were used as washout (no supplement, no pentoxifylline). The two last cycles, 50mL of plain commercial supplement was orally administered. Embryo flushing was carried out eight or nine days after ovulation. Transrectal palpation and ultrasonography were performed daily to assess follicular control, endometrial edema and intrauterine fluid accumulation. Uterine cytology was performed pre and post (24, 48, and 72h) artificial insemination while uterine culture was performed pre and 72h post insemination. Neutrophil counts related to the effects of time did not differ between groups, as well as uterine edema, intrauterine fluid accumulation and positive culture ($P > 0.05$). Embryo recovery was greater in the pentoxifylline group ($P = 0.046$). In conclusion, supplementation with pentoxifylline may be an alternative to decrease the inflammatory endometrial response after artificial insemination and may enhance embryo recovery rate.

Keywords: Mares, embryo transfer, endometritis, fertility, pentoxifylline.

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CAPÍTULO 1

1. INTRODUÇÃO

Com o intuito de aumentar o número de descendentes de animais de alto valor zootécnico para obtenção de futuros atletas e campeões, a espécie equina vem sendo selecionada geneticamente pela performance atlética e não pelo desempenho reprodutivo. Com o avanço da idade de fêmeas campeãs e produtoras, os índices reprodutivos caem juntamente com a fertilidade, fazendo com que as técnicas de reprodução assistida sejam cada vez mais estudadas e utilizadas para minimizar os efeitos do envelhecimento sobre a anatomia e barreiras de proteção naturais do trato reprodutivo da égua, bem como para reduzir os danos causados pela resposta imune uterina exacerbada em éguas susceptíveis (Ignácio et al., 2021).

A resposta inflamatória uterina após inseminação é fisiológica e transitória, todavia pode se tornar intensa e prolongada nas éguas susceptíveis (Segabinazzi et al., 2021). A presença de acúmulo de fluido intrauterino 24 a 48 horas após inseminação classifica a égua clinicamente como susceptível à endometrite (Canisso et al., 2016).

Éguas susceptíveis a endometrite persistente pós cobertura não são capazes de eliminar o processo inflamatório entre 48 e 72 horas após inseminação e podem apresentar repetição de cio, acúmulo de fluido intrauterino pré ou pós inseminação, edema uterino exacerbado, grande número de neutrófilos polimorfonucleares, predispondo o útero á infecções (Tongu et al., 2021; Bucca et al., 2008).

Após 5.5-6.5 dias da fertilização, o conceito chega ao útero (Betteridge et al., 1982). Todavia, a presença de produtos inflamatórios, fluido e bactérias torna o microambiente uterino incompatível com a sobrevivência embrionária e manutenção da prenhez (Troedsson., 1999).

De grande impacto econômico à indústria equina, a endometrite é a terceira enfermidade mais comum que acomete os equinos, a maior causa de redução de fertilidade e está associada a falha na concepção e perda embrionária precoce (Díaz-Bertrana et al., 2021; Segabinazzi et al., 2020).

Os nutracêuticos tem sido amplamente utilizados para melhorar os índices reprodutivos e incluem suplementos, vitaminas, minerais, bioprodutos e substâncias farmacêuticas. Porém, o resultado dessa suplementação é variável e sofre influências individuais e ambientais (Freitas et al., 2018).

A pentoxifilina promove o aumento do remodelamento das hemácias permitindo aumento na circulação e vascularização de diversos tecidos no organismo (Brisko et al., 2011); possui efeito antioxidante e anti-inflamatório (Pollice et al., 2001) e reduz a resposta inflamatória (Pozor., 2011), podendo facilitar o desempenho uterino frente à inflamação, e desta forma, diminuir a colonização de bactérias (Baumgartner, 2007).

O presente trabalho buscou revisar e avaliar os efeitos da pentoxifilina sobre a reação inflamatória após inseminação artificial e taxa de recuperação embrionária em éguas idosas que apresentam endometrite persistente pós cobertura.

2. REVISÃO DE LITERATURA

2.1. Endometrite

A endometrite pode estar associada a infecção por bactérias e fungos ou sêmen após inseminação, tornando-se de natureza multifatorial, o que dificulta o diagnóstico (Canisso et al., 2016).

De acordo com Ferris (2017) o útero da égua sadia tem capacidade de limpeza contra bactérias e fungos sem desenvolver infecção, porém, torna-se susceptível quando há alguma falha nos mecanismos de defesa do organismo, como má conformação perineal, esfíncter vestibulo vaginal danificado, defeito de cérvix, útero penduloso ou com saculação ventral, má condição/score corporal, atividade miometrial prejudicada ou defesa imunológica deficiente (Troedsson et al., 2018).

Após 30 minutos da deposição de sêmen no lúmen uterino, o sistema imune responde com quimiotaxia e ativação dos neutrófilos, com o intuito de fagocitar debris, bactérias e células espermáticas não viáveis (Canisso et al., 2016). Todavia, o pico da inflamação endometrial após inseminação ocorre

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