UNIVERSIDADE FEDERAL DE SANTA MARIA
CENTRO DE CIÊNCIAS RURAIS
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA VETERINÁRIA

Antônio Alcemar Beck Júnior

EFEITO DA SEDAÇÃO COM XILAZINA E BUTORFANOL SOBRE A AVALIAÇÃO DE CLAUDICAÇÃO NOS MEMBROS PÉLVICOS DE EQUINOS

Santa Maria, RS
2018

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Dissertação apresentada ao Curso de Mestrado do Programa de Pós-Graduação em Medicina Veterinária, Área de Concentração em Cirurgia e Clínica Veterinária, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para obtenção do grau de **Mestre em Medicina Veterinária.**

Orientador: Prof. PhD. Flávio Desessards De La Côrte

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2018

Beck Júnior, Antônio Alcemar
Efeito da sedação com xilazina e butorfanol sobre a avaliação de claudicação nos membros pélvicos de equinos / Antônio Alcemar Beck Júnior.- 2018.
46 p.; 30 cm

Orientador: Flávio Desessards De La Côrte
Dissertação (mestrado) - Universidade Federal de Santa Maria, Centro de Ciências Rurais, Programa de Pós Graduação em Medicina Veterinária, RS, 2018

1. Agonista alfa-2 adrenérgico 2. Opióide 3. Claudicação induzida 4. Lameness Locator I. De La Côrte, Flávio Desessards II. Título.

Sistema de geração automática de ficha catalográfica da UFSM. Dados fornecidos pelo autor(a). Sob supervisão da Direção da Divisão de Processos Técnicos da Biblioteca Central. Bibliotecária responsável Paula Schoenfeldt Patta CRB 10/1728.

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Santa Maria, RS
2018

DEDICATÓRIA

Aos meus pais, Antônio Alcemar e Janete Beck por não medirem esforços para a realização dos meus sonhos. Obrigado pelo incentivo ao estudo, pois este foi o melhor presente que poderiam ter me dado.

Ao meu irmão Lorenzo Beck, que junto deles é fonte perene de carinho e amor.

À minha amada namorada e futura colega de profissão, Stephanie Lanzarini Abati, pelo amor e incentivo incessantes. Agradeço seu imenso apoio às minhas decisões e sua compreensão ímpar nos momentos de ausência que a profissão nos proporciona.

Aos cavalos de ontem, hoje e amanhã, por de alguma forma marcarem minha trajetória e serem a razão maior do meu esforço.

AGRADECIMENTOS

A Deus, pelo dom da vida e por guiar meus caminhos.

À Universidade Federal de Santa Maria, pela formação nos cursos de graduação e pós-graduação.

Ao meu orientador, professor Flávio Desessards De La Côrte, pela confiança, aprendizado, criticismo positivo e idealização deste trabalho.

À minha co-orientadora, professora Karin Erica Brass, pelos ensinamentos e grande contribuição no desenvolvimento desta pesquisa.

Aos colegas de pós-graduação, Camila Cantarelli, Grasiela de Bastiani, Marcos da Silva Azevedo, Miguel Gallio e Roberta Pereira, pela amizade, troca de experiências e pelo convívio diário que certamente tornou esta jornada mais agradável. E em especial aos colegas Stéfano Leite Dau e Gabriele Biavaschi, por seu auxílio direto no delineamento e demais etapas deste experimento.

À equipe de colaboradores do grupo de Medicina Esportiva Equina da UFSM, pelo auxílio na execução deste projeto.

A CAPES, pelo apoio financeiro durante a realização do mestrado.

Ao 1º Regimento de Cavalaria Montada da Brigada Militar do Rio Grande do Sul e à Divisão de Cavalaria do Campo de Instrução do Exército Brasileiro, por ceder os animais utilizados neste experimento.

RESUMO

EFEITO DA SEDAÇÃO COM XILAZINA E BUTORFANOL SOBRE A AVALIAÇÃO DE CLAUDICAÇÃO NOS MEMBROS PÉLVICOS DE EQUINOS

AUTOR: Antônio Alcemar Beck Júnior
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Os bloqueios anestésicos perineurais e intra-sinoviais são importantes ferramentas usadas no diagnóstico de claudicações com origem no membro pélvico. Para uma aplicação segura e adequada do anestésico é comum a utilização de contenção química, sobretudo em animais de comportamento agitado. Entretanto, alguns veterinários relutam em utilizar sedativos para facilitar a realização do procedimento, pois acreditam que os efeitos analgésicos e proprioceptivos desses fármacos possam atenuar a intensidade da claudicação. Dessa forma, o propósito deste estudo foi avaliar se o efeito da sedação com xilazina (0,3 mg/kg) ou xilazina associada ao butorfanol (0,01 mg/kg) atenuou a claudicação induzida nos membros pélvicos de equinos. Foram selecionados 12 cavalos adultos (9 fêmeas e 3 machos) que através de exame físico e avaliação objetiva com sensores inerciais foram considerados livres de claudicação. Braçadeiras de aço galvanizado foram posicionadas ao redor do casco e apertadas para induzir claudicação temporária e reversível. Os cavalos foram alocados aleatoriamente em um modelo "crossover" (xilazina, xilazina com butorfanol e controle não-tratado) As avaliações objetivas de claudicação foram realizadas imediatamente antes da administração do sedativo e 20 (T1), 30 (T2) e 40 minutos (T3) após a sedação. A qualidade da sedação foi avaliada nos mesmos momentos, através de uma escala descritiva física e comportamental, além da mensuração da altura da cabeça em relação ao solo (ACRS). Todos os animais demonstraram sinais clínicos de sedação nos primeiros 20 minutos pós-sedação, sugerindo que essas drogas seriam uteis na contenção química para analgesia diagnóstica. A avaliação da melhora na claudicação após a sedação foi realizada usando o teste ANOVA com medidas repetidas e o teste de Bonferroni ($p<0,05$). Não houve diferença na assimetria pélvica entre os grupos xilazina, xilazina com butorfanol e controle nos tempos avaliados. A sedação com xilazina isoladamente ou associada ao butorfanol nas doses recomendadas pode ser utilizada como contenção química para auxiliar a realização de bloqueios anestésicos no membro pélvico sem diminuir a intensidade da claudicação até 40 minutos pós-administração.

Palavras-chave: Cavalo. Agonista alfa-2 adrenérgico. Opióide. Claudicação induzida. Lameness Locator.

ABSTRACT

EFFECT OF SEDATION WITH XYLAZINE AND BUTORPHANOL ON THE EVALUATION OF HINDLIMB LAMENESS IN HORSES

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Perineural and intrasynovial anesthetic blocks are important tools used in the diagnosis of hindlimb lameness. On uncooperative horses, chemical restraint is commonly used for safe and correct anesthetic injection. However, many veterinarians are reluctant to use sedatives to facilitate the procedure because they believe that its analgesic and proprioceptive effects might attenuate the lameness intensity. In this way, the purpose of this study was to investigate whether the sedation with xylazine (0.3 mg/kg) alone or in association with butorphanol (0.01 mg/kg) attenuated the induced hindlimb lameness in horses. Twelve adult horses (9 mares and 3 geldings) considering lameness-free after physical examination and objective lameness assessment with inertial sensors were included in the study. Galvanized steel clamps were placed around the hoof wall and tightened to induce reversible lameness. Horses were randomly allocated in a crossover design (xylazine, xylazine with butorphanol and untreated control). The objective lameness evaluations were performed right before sedation and 20, 30 and 40 minutes after sedation. The quality of sedation was assessed on the same occasions, using a physical and behavioral descriptive scale, and also by measurement of the head height above ground (HHAG). All horses showed clinical signs of sedation during the first 20 minutes after drug injection, indicating that these drugs would be useful as chemical restraint for diagnostic analgesia. The evaluation of lameness improvement after sedation was performed using the repeated measures ANOVA test followed by the Bonferroni's multiple comparison test ($p<0.05$). There was no difference in pelvic asymmetry between xylazine, xylazine with butorphanol and control groups at the different evaluation times. Sedation with xylazine alone or associated with butorphanol at the recommended doses, may be used as chemical restraint method to perform anesthetic blocks on the hindlimb without decreasing lameness intensity until 40 minutes following administration.

Keywords: Horse, Alpha-2 agonist, Opioid, Induced lameness, Lameness Locator.

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1 INTRODUÇÃO

O baixo desempenho esportivo em equinos normalmente tem relação direta com problemas de origem musculoesquelética e cardiorrespiratória (MARTIN Jr. et al., 2000), sendo os problemas relacionados à claudicação responsáveis pelo maior percentual de queda de rendimento e aposentadoria esportiva precoce (ROSSDALE et al., 1985). Claudicações com origem nos membros pélvicos estão diretamente relacionadas ao tipo de atividade esportiva desenvolvida pelo cavalo. Animais destinados a provas de salto, adestramento, rédeas, tambor, rodeio e provas funcionais da raça crioula (LEWIS, 2001; NOBLE, 2001; BAXTER et al., 2003; DABAREINER et al., 2005; ABREU et al., 2011) são submetidos a uma carga de trabalho maior sobre os membros pélvicos, aumentando a incidência de lesões por repetição nessas estruturas (BAXTER et al., 2003).

No exame de claudicação somente a analgesia diagnóstica, realizada através de bloqueios anestésicos perineurais ou intra-sinoviais, indica ao clínico a localização correta e confirma a origem da dor (KANEPS, 2004). Entretanto, cavalos mais agitados ou agressivos tendem a dificultar a realização desses procedimentos, sobretudo aqueles envolvendo os membros pélvicos, representando um risco ao veterinário e seus colaboradores (BUCHNER et al., 1993). Dessa forma, a contenção química desses animais é frequentemente necessária para aumentar a segurança e execução adequada da técnica. Protocolos utilizando agonistas α2-adrenérgicos, tais como a xilazina têm se mostrado úteis neste intuito (RETTIG et al., 2015), apesar de alguns profissionais demonstrarem insegurança em usar fármacos dessa classe, devido às suas propriedades analgésicas e efeitos proprioceptivos como ataxia, miorelaxamento e diminuição da resposta a estímulos (PILSWORTH & DYSON, 2015; MASON, 2015).

Grande controvérsia é observada entre resultados de estudos clínicos e relatos de profissionais experientes sobre a possibilidade de a sedação prévia com essas drogas interferir com a avaliação de claudicação. Buchner e colaboradores (1993) afirmam não haver influência da sedação prévia no grau de claudicação em cavalos com claudicação clínica nos membros torácicos, enquanto Pilsworth & Dyson (2015) demonstram relutância em aplicar esse tipo de contenção por observações pessoais de alteração na marcha e intensidade da claudicação durante avaliação subjetiva. Estudos mais recentes, utilizando avaliação objetiva, demonstram que o uso de xilazina não interfere no padrão da marcha (AZEVEDO et al., 2015), entretanto pode apresentar interferência em claudicações sutis, exigindo atenção especial ao uso dessa droga (RETTIG et al., 2015).

Neste sentido, devido à discordância de resultados observados na literatura aliada à falta de estudos envolvendo especificamente claudicações em membros pélvicos, o objetivo deste estudo foi investigar por meio de avaliação objetiva os efeitos potenciais da sedação com cloridrato de xilazina (0,3 mg/kg) isoladamente ou associada ao tartarato de butorfanol (0,01 mg/kg) sobre a claudicação induzida nos membros pélvicos de equinos.

2 REVISÃO BIBLIOGRÁFICA

2.1 Claudicação

A claudicação é a manifestação clínica mais observada nas lesões do sistema musculoesquelético dos equinos, sejam de natureza muscular, tendínea, ligamentar ou osteo-articular. Consiste também em uma das principais razões de perdas econômicas na indústria do cavalo, devido a fatores como diminuição no número de dias de treinamento, encerramento precoce da carreira atlética e queda de desempenho (WEISHAUPT et al., 2008). Segundo Lindner et al. (1993) a claudicação foi responsável por 57% de fracasso durante os treinamentos em cavalos de corrida, enquanto Hernandez & Hawkins (2001) apontam esse fator como causa de retirada de animais por até 26 dias de sua rotina de treinos.

Devido à diversidade de condições que podem provocar alteração na marcha, e consequentemente claudicação, é fundamental avaliar corretamente o aparelho locomotor, visando reconhecer e localizar a origem da dor (ROSS, 2011). Diante disso, o reconhecimento precoce de enfermidades do sistema locomotor desempenha um papel essencial na medicina esportiva, impedindo o agravamento da condição e lesões catastróficas decorrentes da mesma (WEISHAUPT, 2008).

Os membros torácicos recebem de 60 a 65% do peso do cavalo e seu cavaleiro durante a locomoção, enquanto os membros pélvicos são usados para gerar o movimento de impulsão do animal para frente (REDDING, 2012). Algumas disciplinas esportivas requerem uma adaptação dessa relação durante o movimento, promovendo uma distribuição maior de peso sobre os membros pélvicos. Em particular, atividades como salto, adestramento, apartação, tambor, rodeio e as tradicionais provas funcionais da raça crioula (LEWIS, 2001; NOBLE, 2001; BAXTER et al., 2003; DABAREINER, 2005; ABREU et al., 2011) exigem essa mudança, o que, sem dúvida, aumenta a incidência de lesões nos membros pélvicos, que, por sua vez, se manifestam como queda de performance, mudanças comportamentais e claudicação em diferentes graus.

A claudicação é uma manifestação clínica, porém seu reconhecimento, localização, caracterização e tratamento são complexos (ROSS, 2011). Dessa forma, é fundamental a execução correta e sistemática das etapas do exame de claudicação, no intuito de definir o membro acometido, as estruturas afetadas, o diagnóstico adequado e o prognóstico (BAXTER, 2011). Em casos onde os sinais clínicos não são suficientes para indicar com precisão o local da dor, somente a analgesia diagnóstica poderá indicar a origem da mesma e, consequentemente, dar apoio diagnóstico através da eliminação da dor, componente primário da claudicação (BAXTER & STASHAK, 2011). Este procedimento rotineiro para identificar a origem da dor é realizado através de bloqueios anestésicos perineurais ou intra-sinoviais (articulações, bursas e bainhas tendíneas) (KANEPS, 2004).

2.1.2 Avaliação subjetiva de claudicação

O rotineiro e tradicional exame de claudicação é centrado no prévio conhecimento do clínico das técnicas de semiologia, patologia do sistema locomotor e alternativas de diagnóstico por imagem, onde na maioria dos casos é suficiente a avaliação visual, por parte do médico veterinário, do animal se deslocando em linha reta, ao passo e ao trote (KEEGAN, 2011). Os critérios mais importantes a serem avaliados nesse método, que chamamos de metodologia subjetiva, são a assimetria no movimento vertical da cabeça por ocasião do apoio de cada membro anterior e alterações na simetria dos movimentos verticais das tuberosidades coxais. Estudos cinemáticos da marcha demonstraram que a amplitude desses movimentos são os melhores indicadores para detectar claudicações nos membros torácicos e pélvicos, respectivamente (BAXTER, 2011).

A escala elaborada pela Associação Americana dos Veterinários de Equinos (AAEP, 1991) é mundialmente utilizada no intuito de graduar subjetivamente a intensidade da claudicação por ocasião do exame, sendo diretamente dependente da experiência do examinador:

0 – Sinais de claudicação não são detectáveis sob qualquer circunstância;

1 – Claudicação inconsistente ao trote, difícil de identificar sob qualquer circunstância;

2 – Claudicação inconsistente ao passo ou ao trote em linha reta, porém aparente em algumas circunstâncias;

3 – Claudicação consistente observada ao trote em qualquer circunstância;

4 – Claudicação óbvia ao passo com assimetria visível de movimentos da cabeça e/ou garupa e/ou encurtamento da passada;

5 – Claudicação óbvia com apoio mínimo do membro afetado durante o movimento ou relutância em se mover (KANEPS, 2004).

O membro acometido é mais facilmente detectado quando seu grau de claudicação é moderado a severo. Entretanto, quando é discreto ocorre grande discordância entre os avaliadores, tanto ao identificar como ao graduar a claudicação (KEEGAN et al. 2010). Há também evidências experimentais de que a experiência do avaliador pode influenciar a observação correta e a mensuração subjetiva do grau de claudicação (MARQUÉS et al., 2014). Claudicações mistas, movimentos compensatórios de membros contralaterais ou mesmo acenos aberrantes da cabeça ou da garupa do animal também contribuem para a menor acurácia deste exame.

No campo da pesquisa, a avaliação subjetiva de claudicação é amplamente utilizada para investigar os mais diversos aspectos que envolvem a claudicação, sendo parâmetro, por exemplo, para avaliação de métodos diagnósticos (TURNER, 1989; SCHUMACHER et al., 2004) e resposta a tratamentos (FRIESBIE et al, 2009; GUASCO et al., 2012).

2.1.3 Avaliação objetiva de claudicação

Nos últimos anos, vários estudos desenvolvendo métodos objetivos de avaliação de claudicação sugiram na tentativa de atenuar as limitações encontradas na avaliação subjetiva. Inicialmente, tais métodos se baseavam em estudos de cinemática (avaliação do movimento desprezando a ação das forças), onde o cavalo é submetido ao trote em uma esteira ou através da análise cinética (mensuração das forças do movimento), com a utilização de uma placa estacionária. Embora sejam tecnologias valiosas, o custo elevado dos equipamentos, bem como a necessidade de instalações apropriadas e de coletas repetidas de dados para o ajuste correto do casco na superfície da plataforma, tornam seu uso incomum e inviável na rotina prática (KEEGAN, 2007; KEEGAN, 2011b; WILSON, 2010).

Devido às limitações dos métodos supracitados, foram desenvolvidas alternativas mais práticas para o uso na rotina clínica. Dentre elas se destaca a avaliação por sensores inerciais sem fio, desenvolvida para suprir a necessidade de um equipamento mais barato que os anteriormente citados e que exigisse menor instrumentação do animal e maior portabilidade. Essas características possibilitam seu uso em condições de campo, reduzindo o tempo de exame e a influência do aparelho nos movimentos do animal (KEEGAN et al., 2004; KEEGAN, 2011a).

2.1.3. 1 Avaliação de claudicação por sensores inerciais sem fio

Este é um sistema desenvolvido por veterinários e engenheiros da Universidade do Missouri (EUA) em colaboração com o Instituto de Tecnologia de Hiroshima (Japão), destinado à avaliação objetiva de claudicação por parte dos clínicos de equinos, sendo útil na detecção de alterações sutis no padrão da marcha. Esse sistema consiste de três sensores inerciais sem fio (dois acelerômetros e um giroscópio) conectados a um computador portátil que recebe e analisa os dados. (KEEGAN, 2011a). Os acelerômetros são posicionados na cabeça e na linha média da tuberosidade sacral, enquanto o giroscópio é fixado no aspecto dorsal da quartela do membro torácico direito. Esses dispositivos mensuram a aceleração vertical da cabeça e da pelve e a velocidade angular do membro anterior direito, respectivamente, transmitindo esses dados para o computador portátil. Algoritmos específicos, desenvolvidos a partir de estudos prévios de cinemática, são utilizados neste sistema para detectar e quantificar a claudicação nos membros torácicos e pélvicos (KEEGAN, 2011a).

Este sistema é capaz ainda de desprezar movimentos aleatórios, atribuídos a acenos erráticos da cabeça e da pelve. A claudicação é detectada através da proporção entre os movimentos naturais da cabeça e da pelve e os movimentos gerados pelo desconforto. Além disso, é possível mensurar a claudicação dos membros torácicos e pélvicos através das médias e desvio padrão entre a altura máxima e mínima da cabeça e da pelve, respectivamente. Os resultados são apresentados na forma de gráficos, ilustrando a amplitude do impacto e da propulsão de cada passada (KEEGAN, 2011a).

Esse *software* é extremamente útil na interpretação de claudicações compensatórias ou mistas, através da distribuição do impacto e da elevação dos quatro membros. Ademais, é possível mensurar a melhora do grau da claudicação após bloqueios anestésicos ou tratamentos, assim como a exacerbação do desconforto após os testes de flexão (KEEGAN, 2011a). Por essas razões, além de dispensar equipamentos dispendiosos como esteiras ou instalações específicas, esse sistema surge como uma excelente ferramenta para o médico veterinário de equinos que busca um diagnóstico de claudicação qualificado e precoce.

2.2 Indução de claudicação

Diversos estudos clínicos foram desenvolvidos para avaliar métodos diagnósticos (VORSTENBOSH et al., 1997; SCHUMACHER et al., 2014) ou intervenções terapêuticas (DOUCET et al., 2008; KOENE et al., 2010) em equinos naturalmente claudicantes. Entretanto, claudicações naturais possuem alto grau de complexidade e características indesejáveis no desenvolvimento de estudos clínicos, sobretudo no que diz respeito ao controle de sua intensidade, duração e consistência. Essas características aumentam a dificuldade em selecionar inúmeros equinos com a mesma natureza ou grau de claudicação (SWAAB, 2015). Dessa forma, diversas técnicas vêm sendo avaliadas ao longo dos anos visando induzir claudicação reversível em animais sadios, reduzindo a variabilidade observada em animais naturalmente claudicantes. Um método consagrado é a indução de sinovite através da administração intra-articular de um antibiótico associado ao dimetilsulfóxido (McILWRAITH & VAN SICKLE, 1981) ou de sangue autógeno como indutor de sinovite sutil a moderada (JUDY & GALUPPO, 2005). Palmer & Bertone (1994) induziram sinovite em 10 articulações de seis cavalos, utilizando injeções intra-articulares de lipopolissacarídeos provenientes da parede celular de bactérias *E. coli*, em um modelo experimental descrito previamente em pôneis (FIRTH et al., 1987; FIRTH et al., 1988). A citocina IL-1β desempenha papel fundamental em inflamações sinoviais de ocorrência natural, por isso também tem sido utilizada para induzir sinovite e consequente claudicação experimental (DePUY et al., 2007; TÓTH, et al., 2014). Somado a esses, Thomsen et al. (2010) induziram dor em cavalos sadios através da distensão da articulação metacarpofalangeana com solução salina. Essas técnicas, apesar de sua eficiência em induzir uma claudicação temporária, possuem alguns inconvenientes, tais como a alta variabilidade no começo, duração e grau de claudicação obtidos (SWAAB, 2015).

Métodos menos invasivos foram desenvolvidos na intenção de aplicar forças ajustáveis no casco, seja através de parafusos e porcas na porção interna de uma ferradura modificada para pressionar a sola (MERKENS & SCHAMHARDT, 1988) ou da colocação de um parafuso no ápice de uma ferradura em formato de coração para pressionar diretamente a região da ranilha (FOREMAN & LAWRENCE, 1991). Apesar de esses métodos serem mais facilmente controlados e revertidos que as técnicas de injeção intra-articular (FOREMAN & LAWRENCE, 1991), algumas deficiências também foram observadas. Schumacher et al. (2000) constataram claudicação residual no método de pressão sobre a sola, dependendo do local de aplicação dos parafusos. Segundo os mesmos pesquisadores, parafusos rombos produzem maior claudicação residual quando comparados a parafusos pontiagudos. Com relação à técnica de pressão sobre a ranilha, Keegan et al. (2000) comentam que cavalos submetidos ao trote em esteira demonstraram um padrão de claudicação inconsistente no decorrer das avaliações.

Um método alternativo para indução de claudicação temporária se utiliza de braçadeiras de aço inoxidável ajustadas de modo a aplicar pressão ao redor do casco, impedindo assim sua expansão. Esse procedimento foi inicialmente descrito por Stick & Caron (1994) e teve seu uso aperfeiçoado e validado por estudos posteriores (SWAAB, 2015; SILVA et al. 2015), demonstrando sua capacidade de induzir claudicação com reversão após a retirada do dispositivo. O presente estudo utilizou esta técnica para suscitar claudicação grau 3-4/5 (AAEP) nos membros pélvicos de equinos sadios.

2.3 O uso de sedativos na avaliação de claudicação

Para a contenção química de cavalos submetidos a bloqueios anestésicos, é consagrado o uso de fármacos sedativos como, por exemplo, o cloridrato de xilazina, ou comumente xilazina. Este sedativo pertence à classe dos agonistas α2-adrenérgicos, cujos efeitos farmacológicos em medicina equina são bem descritos. Sua aplicação intravenosa resulta em sedação dose-dependente, analgesia e miorelaxamento, com efeitos marcantes sobre o sistema nervoso central, tais como ataxia, abaixamento da cabeça, diminuição da atividade locomotora e da resposta à estímulos (ENGLAND, CLARKE & GOOSSENS, 1992; MASON, 2004). A xilazina é efetiva em diversas doses, com a de 0,5 mg/kg considerada satisfatória e 1,0 mg/kg usada quando uma sedação mais profunda é necessária (TAYLOR & CLARKE, 2007). Trabalhos anteriores utilizando sensores inerciais para mensurar claudicação avaliaram a influência da sedação com xilazina em doses semelhantes à proposta por este estudo. Rettig et al. (2015) propuseram o uso deste agonista α2-adrenérgico na dose de 0,3 mg/kg, enquanto Azevedo et al. (2015) utilizaram 0,25 mg/kg. Ambos os estudos utilizaram animais sadios ou naturalmente claudicantes e obtiveram sedação satisfatória. Entretanto, Rettig et al. (2015), sugerem cuidado ao se utilizar xilazina em animais com claudicação leve, indicando possível interferência do referido fármaco na avaliação.

O butorfanol é um fármaco opióide agonista-antagonista, sendo o mais amplamente utilizado em equinos dentre os membros dessa classe. Seu uso primário visa sua propriedade analgésica, entretanto frequentemente é utilizado em associação com um fármaco sedativo, produzindo excelente sedação química para procedimentos em estação ou como parte de protocolos pré-anestésicos e um adjunto à contenção química (MASON, 2004). A combinação de xilazina com butorfanol é comumente administrada por via intravenosa nas doses de 0,5-1,0 mg/kg e 0,02 mg/kg, respectivamente (TAYLOR & CLARKE, 2007). O butorfanol é capaz de diminuir dor superficial e visceral, além dos sinais clínicos de dor pós-operatória em cavalos submetidos a cirurgias ortopédicas (SELLON et al., 2001; KNYCH et al., 2013). Os mesmos autores relatam que, além de diminuir a frequência dos borborigmos intestinais, essa droga apresenta efeitos proprioceptivos e comportamentais como ataxia e estimulação da atividade locomotora.

3 ARTIGO

TRABALHO A SER SUBMETIDO PARA PUBLICAÇÃO
Periódico: Journal of Equine Veterinary Science

EFFECT OF XYLAZINE AND BUTORPHANOL ON EXPERIMENTAL HINDLIMB LAMENESS IN HORSES

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Abstract

Anesthetic blocks of hindlimb joints play a fundamental role in the diagnosis of conditions affecting these sites. However, some restless horses can turn this procedure a lot difficult. Many clinicians believe that the use of chemical restraint to facilitate joint injections may interfere with the lameness intensity due to its analgesic and proprioceptive effects. The aim of this study was to assess whether sedation with xylazine hydrochloride alone or associated with butorphanol tartrate ameliorate or even abolish induced hindlimb lameness. Intravenous injection of xylazine (0.3 mg/kg) alone **(XG)** or associated with butorphanol (0.01 mg/kg) **(XBG)** were given randomly to 12 adult horses. A third control group **(CG)** was left untreated. Using a crossover design, all horses participated of all groups. Lameness induction was performed with the placement of a circumferential metal clamp causing pressure on the hoof wall. Sedation was assessed using a descriptive physical and behavioral scale and also by the head height above ground (HHAG) prior to the treatment (0 min) and 20, 30 and 40 minutes following treatment. In order to eliminate experience-related errors during in the lameness evaluation, objective lameness evaluations were performed before sedation (baseline after lameness induction), and at 20, 30 and 40 minutes post-sedation. Baseline lameness after induction values of P_{max} obtained on the objective assessment were 10.3±5.43 mm **(XG),** 9.5±1.83 mm **(XBG)** and10.74±4.68 mm **(CG)** and 9.12±3.62 mm and P_{min} mean values of 9.22±2.86 mm **(XG)**, 7.1±3.13 **(XBG)** and 9.12±3.62 mm **(CG)** and were used to calculate the amount of alteration on pelvic asymmetry after sedation (lameness improvement (LI)). All horses showed clinical signs of sedation 20 minutes post drug injection, indicating that these drugs would be useful to chemical restraint for diagnostic analgesia. Lameness improvement after sedation was evaluated using the repeated measures ANOVA followed by the Bonferroni's test ($p<0.05$). There was no difference in pelvic asymmetry between xylazine, xylazine with butorphanol and untreated control group at the different evaluation times. Spearman's correlation test showed that there was no correlation between the factors HHAG and LI (r=-0.040). Xylazine alone or associated with butorphanol at the recommended doses, may be used as chemical restraint to turn an anesthetic block on the hindlimbs a safer procedure without masking lameness intensity until 40 minutes post administration.

Keywords: horse, alpha-2 agonist, opioid, induced lameness, Lameness Locator

1. Introduction

Hindlimb lameness is a very common cause of reduced performance or premature retirement in sport horses [1, 2]. Weight redistribution and chronic repetitive compression caused by overloading of the hindlimbs during exercise increases the incidence of hindlimb injuries in some breeds and disciplines [3], like show jumping, dressage, eventing, western performance and Brazilian Crioulo horses [4-8]. Intrasynovial and perineural analgesia are an important part of the lameness examination and commonly used to localize and confirm the pain source [9]. However, this procedure may be difficult and may represent an occupational risk to the clinician, mainly due to uncooperative or more irritable horses. Thus, chemical restrain is often used to increase safety during the procedure. Sedation with alpha-2 agonists such as xylazine alone or combined with butorphanol prior the synoviocentesis of the hock has been shown useful to facilitate the procedure [10]. Nevertheless, some veterinarians believe that the analgesic properties and side effects of these drugs, such as low head carriage and resulting ataxia, may interfere with the subsequent interpretation of the anesthetic block and lameness evaluation [10, 11].

Controversial results of clinical studies concerning the influence of sedatives in the lameness examination are found in the literature. For instance, a kinematic study showed that sedation using xylazine in sound horses caused changes in the gait pattern, something that could interfere with the subjective lameness evaluation [12]. Taintor et al. tested detomidine, most potent alpha-2 agonist than xylazine, and also the tranquilization with acepromazine on lame horses without observing effects on the lameness intensity in the objective assessment [13]. Two other studies reported that xylazine alone did not decrease lameness intensity in both fore and hindlimb clinically lame horses [14, 15].

In the research arena, naturally occurring lameness usually presents undesirable variability, as well as difficulty to group horses with the same pain source or lameness intensity. Therefore, various techniques of induced reversible lameness in sound horses have been developed to eliminate this problem [16]. Lameness induction with adjustable steel clamps putting pressure on the hoof wall is one of the experimental lameness induction models already tested, yielding more consistent lameness that is quickly solved with clamp loosening [16, 17].

Considering potential analgesic effects of xylazine at the recommended dose of 0.3 mg/kg and their association with butorphanol at 0.01 mg/kg, the aim of this study was to investigate the potential effect of sedation of these drugs on the assessment of induced hindlimb lameness.

2. Materials and Methods

2.1 Horses and selection criteria

Twelve adult horses, 3 geldings and 9 mares, were selected for this study after physical examination (subjective assessment) and objective evaluation with a body-mounted inertial sensors system. Horses had a mean age of 12.41 ± 4.31 years (range, 7 to 19 years), mean body weight of 516 ± 49.12 kg (range, 436 to 595 kg) and included 4 Brazilian jumping horses and 8 crossbreds. Based on the objective evaluation, only sound horses with DIFFMIN (P_{min}) and DIFFMAX (P_{max}) values up to 3mm (mean ± SD) when trotted in a straight line on a loose sand surface were included in this study.

2.2 Instrumentation

Horses were objectively evaluated using a wireless inertial sensor-based system (LL; Lameness Locator, Columbia, MO, USA). Each horse was instrumented with 3 sensors: one accelerometer on the top of the head attached to a head halter; a second accelerometer on the dorsal midline on the *tuber sacrale*; and one gyroscope on the dorsal aspect of the right front pastern [18]. The first assessment was done prior to the metal clamp application in order to detect lameness-free horses, i.e. – horses showing pelvic asymmetry below the threshold value (3mm), criteria to be included in the study. Then, after a metal clamp was placed around the hoof and tightened, a baseline of lameness severity was obtained. Horses were trotted in a straight line sampling at least 25 strides on a flat sand floor. The objective evaluation (LL) of hindlimb lameness is based in the measurement of pelvic vertical movement asymmetry. The P_{max} and P_{min} variables are reported as the difference (mm) between the highest point of the pelvis after the support of the right hindlimb and the highest point of the pelvis after the support of the left hindlimb and between the lowest point of the pelvis during the support of the right hindlimb and the lowest point of the pelvis during the support of the left hindlimb, respectively [18].

2.3 Lameness induction

All horses had their routine farrier work performed before the study, including balanced trimming and shoeing of the hindlimbs to prevent distal migration of the clamps. The experimental design of reversible lameness induction used was similar to the described by Swaab et al. [16] and modified by Silva et al. [17]. Silva et al. (2015) used this method to promote forelimb lameness while Swaab et al. (2015) used the clamps in both fore and hindlimbs. Galvanized metal clamps were placed around the hoof wall to limit the hoof expansion by the pressure exerted. The hindlimb in which the clamp was attached was chosen randomly. The width of the plantar portion of the clamp was reduced by the half to avoid impingement on the soft tissues of the heel bulbs or coronary band (Figure 1). To prevent the proximal migration of the clamp when tightened, two small metal plates were attached with screws on the dorsomedial and dorsolateral aspect of the hoof wall. A large dorsal screw, used to tighten the clamp, was positioned laterally to prevent trauma during pressure adjustment. The metal clamp was gradually tightened until horses showed a III-IV lameness grade on the AAEP Lameness Scale (I – V) [19] on the subjective assessment and P_{max} and P_{min} values corresponding to a moderate to severe lameness in the LL descriptive scale. After the last trial (40 minutes post-sedation) the clamp was loosened and replaced only before the next treatment. Thirty minutes after removing the clamp all horses were observed again at the trot to evaluate the eventual presence of residual lameness. In cases of residual lameness, the horses would receive rescue analgesia with phenylbutazone (4.4 mg/kg) intravenously.

2.3 Treatment groups

Right after the lameness induction, all horses were randomly selected to receive an intravenous injection of xylazine hydrochloride 10% (0.3 mg/kg; J.A. Animal Health, Patrocinio Paulista, SP, Brazil) **(XG)** or xylazine hydrochloride 10% (0.3 mg/kg) combined with butorphanol tartrate (0.01 mg/kg; Zoetis, Campinas, SP, Brazil) **(XBG)**. A third untreated control group **(CG)** was used to explain possible variations in the lameness intensity overtime. Once sedated, horses were re-evaluated objectively at 20, 30 and 40 minutes to verify post-treatment lameness intensity, totalizing five trials (including baseline after lameness induction and residual lameness evaluation) by group for each horse included in this study. The **CG** followed the same methodology of sedated groups. The horses were handled by the same person at each evaluation time. In a crossover study design, all horses were included in the different treatment groups with a washout period between treatments of at least 48h.

2.4 Assessment of sedation

The quality of sedation was evaluated by one veterinarian that was aware of which group and evaluation time point the horse was in. The assessment was done using a modified simple descriptive scale of 0-3 [20]: **0** - no sedation, horse was alert, with normal posture and response to contact with handler; **1** - mild sedation, low head carriage, relaxed facial muscles and pendulous lower lip; **2** - moderate sedation, head lowered towards ground and swaying of hindlimbs; **3** - marked sedation, attempted or became recumbent, no response to intervention. Additionally, the head height above ground (HHAG) was measured prior to each evaluation time. Right before the sedation, the HHAG was evaluated with a horse height measuring stick from the ground level to the horses' nostrils. The height measured at this moment was used to compare with HHAG values observed at 20, 30 and 40 minutes after treatment as an evaluation of sedation level [21].

2.5. Data analysis

Taking into account that negative values of P_{max} and P_{min} provided by LL only indicate left hindlimb lameness and positive values indicate right hindlimb lameness, a standardization was performed by multiplying all left lame limbs values by -1.

Data collected with LL were analyzed with a special software that use algorithms developed from kinematic studies [18]. The results were interpreted according to manufacturer recommendations. The effect of sedation on P_{max} and P_{min} was evaluated through the lameness improvement percentage (LI) for each time point after sedation (lameness improvement). This value was used to estimate whether lameness severity post sedation increased or decreased by the amount of changes in P_{max} and P_{min}, and was calculated by the ratio of the difference between baseline value and time point value on the baseline value (P before sedation – P after sedation /P before sedation.).

In order to meet the assumptions of the analysis of variance test (ANOVA), all means of LI of each group were converted to the sine-wave function, using SWAVE =(√LI/100). ANOVA followed by Tukey's test was used to compare the HHAG means at different time points to evaluate differences in the sedation level. In turn, repeated measures ANOVA followed by Bonferroni's multiple comparisons test was used to compare the mean HHAG of both treatment groups at different evaluation times, as well as to compare the means of P_{max} and P_{min} lameness intensity after sedation, separately, to investigate whether treatments attenuate lameness severity. Spearman's correlation test was used in order to clarify the correlation between HHAG and lameness improvement rate. Significance was set at $p<0.05$ (GraphPad Prism version 5.0, San Diego, California, USA).

2.6 Ethical considerations

This study was approved by the Ethic Committee on Animal Use of the Federal University of Santa Maria (Protocol number CEUA 4024140617).

3. Results

After tightening the clamp (right before sedation) all 12 animals showed a noticeable and consistent lameness at trot in a straight line, comparable to the subjective lameness evaluation grade III-IV/V [8] and P_{max} mean values of 10.3±5.43 mm **(XG)** and 9.5±1.83 mm **(XBG)** e P_{min} mean values of 9.22±2.86 mm **(XG)** and 7.1±3.13 **(XBG)** on the objective analysis. Regarding the **CG**, P_{max} and P_{min} values were 10.74±4.68 mm and 9.12±3.62 mm at lameness induction, respectively. Moreover, all horses showed head asymmetries at weight bearing on the ipsilateral forelimb, which were considered as compensatory lameness.

All horses receiving xylazine or xylazine/butorphanol association showed signs of sedation 20 minutes after drugs administration (Figure 2). Five horses from **XG** as well as the **XBG** (41.66%) did not present clinical signs of sedation after 20 minutes. Five horses (41.66%) from the **XG** presented head dropping, relaxed facial muscles and pendulous lower lip, compatible with sedation score 1 in the analogic scale (mild sedation), when evaluated at 40 minutes post-treatment. In the **XBG**, four horses (33.33%) showed signs of mild to moderate sedation (score 1: n=3 and score 2: n=1), with head lowered towards ground and swinging of hindlimbs, when evaluated at 40 minutes post-treatment. None of the sedated horses (**XG** and **XBG**) demonstrated features of marked sedation (score 3) at any evaluated time.

Comparing the mean HHAG baseline with the measurements at three time points after sedation no differences were observed in both **XG** and **XBG** ($p>0.05$). Thus, evaluating the head dropping, there was no difference in the sedation intensity between the evaluated time points. Likewise, comparing mean HHAG of **XG** and **XBG** treatment groups at different evaluation times, no difference was observed ($p>0.05$).

There was no correlation between lameness improvement and the head height above ground ($r= -0.040$), showing that there is an insignificant relationship between these two factors (Figure 3).

4. Discussion

This study used a reversible induced lameness model to decrease possible variability that is usually observed in clinical trials formed by sound or naturally lame horses, such as the inconsistence of lameness degree at different evaluation times. This lameness-induced method demonstrated to promote consistent lameness intensity at the baseline that was reversible after clamp removal. The traditional subjective hindlimb lameness evaluation is based on the observation of vertical pelvic movement asymmetry [22]. However, the visual exam of horse's motion often presents low agreement between observers mostly due to the low capacity of the human eye to detect mild and moderate lameness [23]. The choice of an objective evaluation method was to limit interpretation variation of lameness intensity by different evaluators with different training level. As mild changes in pelvic asymmetry also were noted in the **CG**, especially at 30 and 40 minutes after lameness induction, it is possible that a few horses are able to adapt their gait to the use of the hoof clamp instead of meaning lameness improvement.

In chronic hindlimb lameness, such as distal tarsal osteoarthritis, intrasynovial anesthesia indicates the precise source of pain and confirms the initial clinical diagnosis for both clinician and owner [9, 24]. However, some uncooperative horses may represent a serious danger to the assistant or veterinarian and make the procedure much more difficult, mainly in synovial blocks. Therefore, sedation prior to more invasive clinical procedures became an important allied to the practitioner.

The time intervals of 20, 30 and 40 minutes after sedation to evaluate lameness intensity, were chosen to simulate the time needed from the joint injection to achieve full anesthetic effect, which is the usual time to re-evaluate the previously sedated horse when an anesthetic block is performed in the clinical routine [24]. Furthermore, the low head carriage and subjective signs of sedation observed at the early minutes after treatment demonstrated that these protocols probably provided adequate chemical restrain to the achievement of diagnostic analgesia.

Xylazine is the most commonly alpha-2 agonist drug used in equine medicine. The intravenous administration of this drug results in dose-dependent sedation, analgesia and myorelaxation, with marked effects on the central nervous system, such as ataxia, head dropping and decreased response to stimuli [25- 27]. Butorphanol in turn, is a narcotic opiate agonist-antagonist used in equine medicine as an analgesic drug, as an adjunct agent in pre-anesthetic protocols and to chemical restrain [28]. According to the literature, butorphanol ameliorates signs of superficial pain in horses, but it presents some adverse behavioral effects, which include ataxia and stimulation of locomotor activity [28, 29]. A synergistic effect has been reported following the use of xylazine and butorphanol intravenously, producing a deeper level of sedation [28]. Xylazine has been shown to be effective at several doses, being 0.5mg/kg considered satisfactory and 1.0mg/kg used when deeper sedation is required; when associated with xylazine, butorphanol intravenous safe dose varies between 0.01 to 0.02 mg/kg [30]. The short-acting doses of sedation used in this study were chosen to simulate the protocol used in the routinely clinical evaluation.

Despite the above mentioned analgesic properties and proprioceptive side effects, this study has showed that sedation with xylazine and xylazine/butorphanol did not affect the lameness intensity in horses with experimentally induced lameness. However, several clinical studies and lameness experts' opinions concerning the putative effects of sedation on equine lameness [10-15] have been reported divergent results. An earlier study described that 4 lame horses required xylazine sedation to perform the injection of navicular bursa. Despite the small sample, the authors reported no changes in lameness degree due to sedation [31]. Opposing the results of objective evaluation in our study, Pilsworth & Dyson (2015) affirmed that in their personal observation, xylazine in doses as low as 0.15 mg/kg btw is able to decrease or even abolish lameness very quickly in the subjective evaluation of naturally lame horses [11]. In turn, Azevedo and colleagues administered a low dose of xylazine (0.25 mg/kg) or acepromazine 1% (0.025 mg/kg) in clinically lame horses using an objective evaluation method did not observe changes in the lameness manifestation. They reported no influence on the lameness degree or gait pattern. [14]. In agreement to our findings, xylazine used in the same low dose as the one used in this study showed no interference with hindlimb lameness 20 and 60 minutes following sedation on sound, mildly or markedly lame horses. However, may strongly effect the forelimb evaluation up to 60 minutes, especially in mild lameness. Therefore, care must be taken in interpreting diagnostic analgesia in these cases [15]. To the authors' knowledge there are no published reports of the effect of xylazine/butorphanol association in lameness intensity of horses undergoing diagnostic analgesia. This lack of literature was also recently mentioned by De Cozar (2018), which raised question about alpha2-agonists/opioid combination to this purpose [32].

Using an objective evaluation system, high P_{max} absolute values indicate push-off type hindlimb lameness, while high P_{min} absolute values indicate impact-type hindlimb lameness. Because these variables are calculated for every stride, these are the most reliable indicator of hindlimb lameness [19]. In the horses of this study, the greatest rates of lameness improvement at all times occurred with the P_{max}, variable associated with push-off lameness

(Figure 4). If lameness had ameliorated because of previously sedation, probably would have been observed highest changes in the means of P_{min}, which is associated with impact lameness such as caused by the hoof wall clamp pressure.

The lameness improvement rate observed at 40 minutes in both **XG** (35.49±27.88% (P_{max}); 4.56±6.86% (P_{min})) and **XBG** (30.36±35.54% (P_{max}); 13.58±20.91% (P_{min})) did not result from the sedation effects of the treatments. These results are supported by the information provided by Moens et al. (2003) [33], which states that the sedation peak in low dose (0.5 mg/kg) is observed 10 minutes following administration, during no longer than 30 minutes and gradually decreasing up to 60 minutes. In the same way, improved somatic analgesia induced by xylazine/butorphanol association occurs within 10 to 15 minutes, with duration for approximately 30 to 40 minutes [34, 35]. One hour after sedation, horses from both **XG** and **XBG** were free of sedation signs. Likewise, it is unlikely that any effect on the lameness severity should be observed after this period. Moreover, the mean lameness improvement rate observed on both treated groups at 20 minutes after sedation, the time of maximum sedative and analgesic effects, was considered mild (22±19.94% (P_{max}); 8.25±13.57% (P_{min})) for **XG** and (24.18±25.42% (P_{max}); 14.51±18.62% (P_{min})) for **XBG** treatments. We hypothesized that these subtle changes in lameness intensity documented by the motion could be hard to detect on the subjective assessment, this because extrapolating information concerning anesthetic blocks of the hock, a minimum of 60 to 70% improvement in lameness is considered to be a positive response on the subjective assessment [36]. Other important point to emphasize is the wide individual variabilities in the horses' sensitivity to the drugs. Hence, decreases and increases in sedation and lameness degrees can be expected, with individual responses and different clinical signs demonstration. From the practical point of view, the relevance of the results of this study lays in the possibility of veterinarians to use sedation for increase safety in the diagnostic anesthesia of pelvic limbs, without the risk of undesirable losses in the accuracy of the lameness exam. This information contradicts the theory that is always best avoid the sedation if it all possible [37]. Future studies are necessary to provide information on how interactions of butorphanol with others commonly used alpha-2 agonists, such as detomidine and romifidine, can reduce the accuracy of lameness exam after sedation for blocking.

On the basis of our findings, this study supports the use of xylazine and xylazine associated with butorphanol to turn an anesthetic block on the hindlimb a safer procedure without masking the lameness severity until 40 minutes after sedation.

Acknowledgements

The authors would to thank to the Mounted Police of Santa Maria and Cavalry Division of Brazilian Army for their valuable contribution to this project. This study was funded by the Coordination for the Improvement of Higher Education (CAPES) and Foundation to Support Science and Technology (FATEC), agreement FATEC/UFSM (Grant 5.03.0025).

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Figures

Figure 1 – Image representing the dorsolateral (A) and plantar (B) positioning of a circumferential metal clamp in the hoof wall to induce consistent and reversible hindlimb lameness. Note the lateral positioning of the large dorsal screw to avoid injuries (A) and the reduced width of the plantar portion of the clamp to avoid trauma in the heel bulbs and coronary band.

Figure 2 – Horse showing head lowered towards ground compatible with moderate sedation (score 2) at 20 minutes post-sedation (A). The same horse showing head dropping, relaxed facial muscles and pendulous lower lip (sedation score 1) at 40 minutes post-sedation (B). Note the height measuring stick to measure the HHAG from ground level to the horse's nostrils.

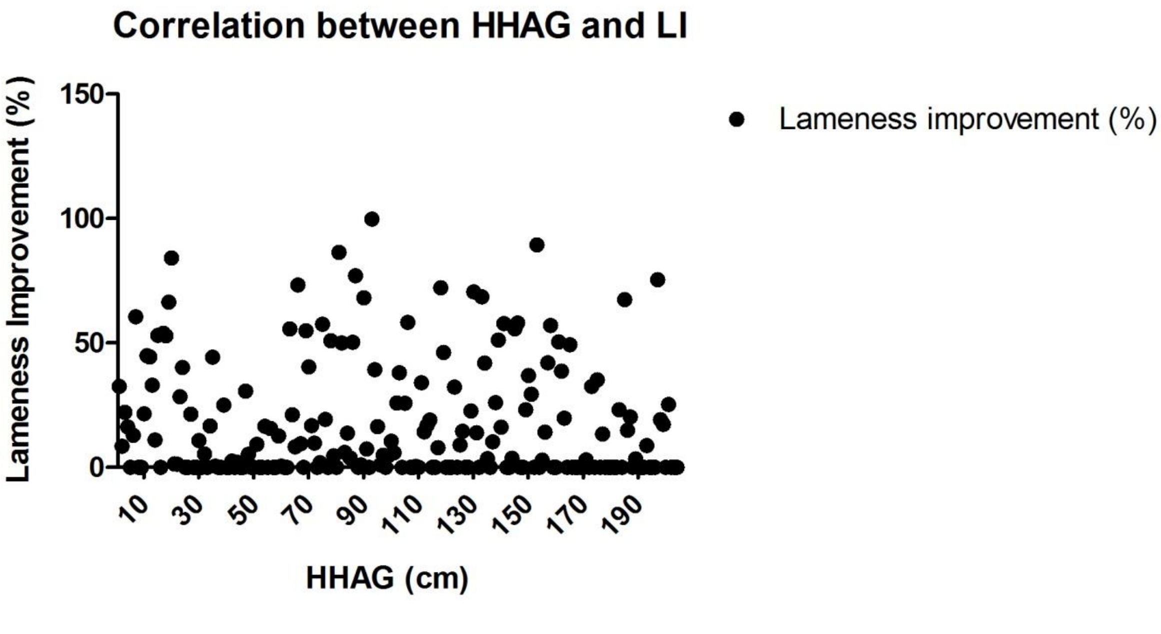

Figure 3 – Relationship between HHAG and lameness improvement rate by Spearman's correlation test. No correlation were found between these two factors (r= -0.040).

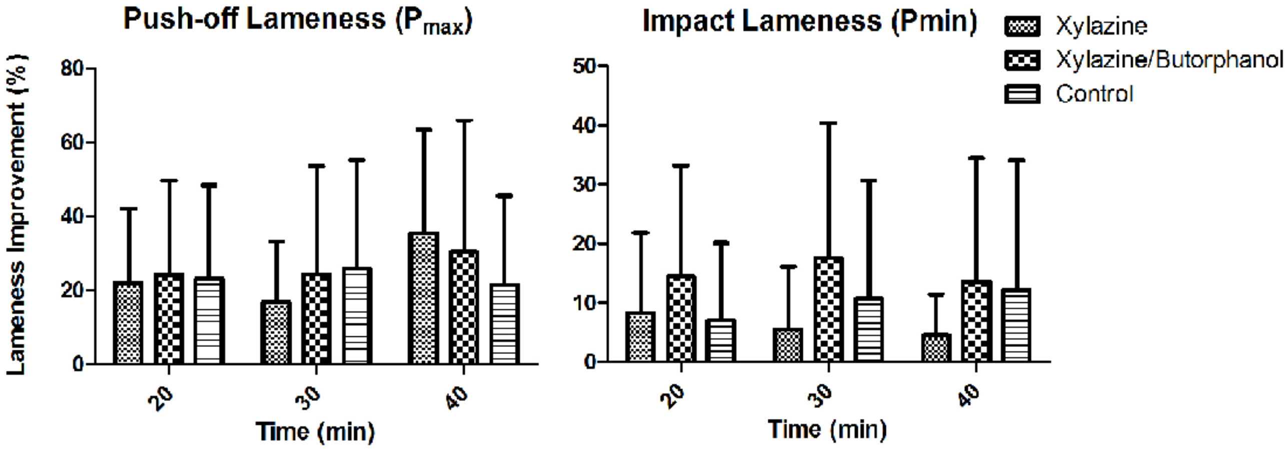

Figure 4 - P_{max} (a) and P_{min} (b) lameness improvement (%). Comparing with baseline lameness some changes in these variables were noted in all time evaluation points, but no differences were seen between groups XG and XBG at 20, 30 and 40 minutes after sedation ($p>0.05$).

4 CONSIDERAÇÕES FINAIS

O emprego de um sistema de avaliação objetiva aderiu confiabilidade aos dados, uma vez que diminui a possibilidade de discordância e erros decorrentes da inexperiência do avaliador. Devido aos valores de desvio padrão elevados na variável melhora de claudicação, novas pesquisas incrementando o número de cavalos poderiam trazer ainda mais confiabilidade aos resultados. Da mesma maneira, novos estudos devem ser desenvolvidos no intuito de investigar o efeito do butorfanol associado a outros fármacos agonistas α2-adrenérgicos comumente usados para facilitar o bloqueio anestésico dos membros pélvicos, como a detomidina e a romifidina.

Dessa forma, os resultados deste estudo apoiam o uso da sedação com xilazina isoladamente ou combinada ao butorfanol nas doses recomendas para facilitar a realização de bloqueios anestésicos no membro pélvico até 40 minutos pós-administração. Do ponto de vista prático, esses achados permitem aos clínicos utilizarem esses fármacos sem o risco de perdas indesejáveis na acurácia de seu exame.

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