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INFUSÃO CONTÍNUA DE DEXMEDETOMIDINA OU XILAZINA COMO PARTE DE PROTOCOLOS BALANCEADOS PARA CADELAS EM CAMPANHAS DE CASTRAÇÃO

DEXMEDETOMIDINE OR XYLAZINE CONTINUOUS RATE INFUSION AS PART OF BALANCED PROTOCOLS FOR BITCHES IN SPAY-NEUTER PROGRAMS

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Dissertação apresentada ao Programa de Pós-Graduação em Ciência Animal, área de concentração Clínica e Cirurgia Veterinária, da Escola de Ciências da Vida da Pontifícia Universidade Católica do Paraná, para obtenção do título de Mestre em Ciência Animal.

Orientadora: Profa. Dra. Cláudia Turra Pimpão

Coorientador: Prof. Dr. Luiz Guilherme Achcar Capriglione

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Programa de Pós-Graduação em Ciência Animal
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ATA Nº 0130 E PARECER FINAL DA DEFESA DE DISSERTAÇÃO DE MESTRADO EM CIÊNCIA ANIMAL DA ALUNA MANOELLA OURIQUE MÜLLER

Aos vinte dias do mês de fevereiro do ano de dois mil e dezenove, às 14horas, realizou-se no auditório FTD Digital Arena, da Pontifícia Universidade Católica do Paraná, localizada no Campus de Curitiba, Rua Imaculada Conceição, nº 1155, Prado Velho – Curitiba – PR, a sessão pública de defesa da dissertação da mestranda Manoella Ourique Müller, intitulada: **"INFUSÃO DE DEXMEDETOMIDINA OU XILAZINA COMO PARTE DE PROTOCOLOS BALANCEADOS PARA CADELAS EM CAMPANHAS DE CASTRAÇÃO"**. A mestranda concluiu os créditos exigidos para obtenção do título de Mestre em Ciência Animal, segundo os registros constantes na secretaria do Programa. Os trabalhos foram conduzidos pela Professora orientadora e Presidente da banca, Dra. Claudia Turra Pimpão (PUCPR), auxiliada pelos Professores Doutores Celina Tie Nishimori Duque (PUCPR) e Juan Carlos Duque Moreno (UFPR). Procedeu-se à exposição da Dissertação, seguida de sua argüição pública e defesa. Encerrada a fase, os examinadores expediram o parecer final sobre a Dissertação, que nos termos do Artigo 53 do Regulamento deste Programa de Pós-Graduação, foi considerada aprovado.

Profa. Dra. Claudia Turra Pimpão (Presidente)
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Proclamado o resultado, a Presidente da Banca Examinadora encerrou os trabalhos, e para que tudo conste, eu Caroline Nocera Bertton, confiro e assino a presente ata juntamente com os membros da Banca Examinadora.

Curitiba, 20 de fevereiro de 2019.

Caroline Nocera Bertton
Caroline Nocera Bertton
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SUMÁRIO

Dedico este trabalho aos meus pais, que com todo o amor do mundo sempre me apoiaram nas minhas decisões.

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LISTA DE ABREVIATURAS

AAHA – *American Animal Hospital Association*

AINEs – anti-inflamatórios não esteroidais

BL – *baseline moment*

BRL – *brazilian real*

BSA – *body surface area*

C – *moment of cervix ligature*

CRI – *continuous rate infusion*

DEX – dexmedetomidina/*dexmedetomidine*

END – *end of surgery – last skin suture*

$EtCO_2$ – pressão parcial de dióxido de carbono ao final da expiração (mmHg)

FC – frequência cardíaca (bpm)

FR – frequência respiratória (mpm)

HR – *heart rate* (bpm)

IC – infusão contínua

INI – *moment of the fist skin incision*

LO – *moment of left ovary ligature*

MAP – *mean arterial pressure* (mmHg)

MPA – medicação pré-anestésica

NMDA – N-metil-D-aspartato

OH – ovariohisterectomia/*ovariohysterectomy*

PAM – pressão arterial média (mmHg)

RO – *moment of right ovary ligature*

RR – *respiratory rate*

RVS – resistência vascular sistêmica

SpO_2 – saturação de oxigênio capilar periférico (%)

Temp – temperatura corporal (˚C)

WSAVA – *World Small Animal Veterinary Association*

XILA – xilazina

XYLA – *xylazine*

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FORMATO DA DISSERTAÇÃO

A presente dissertação é composta por capítulos. O capítulo 1 apresenta uma introdução geral, a contextualização do tema e os objetivos de estudo. O capítulo 2 trata-se de artigo científico completo, contendo referências, e formatado nas normas da revista Journal of the American Veterinary Medical Association (JAVMA). O capítulo 3 finaliza esta dissertação com conclusões gerais e considerações finais deste trabalho e sugestões para estudos futuros. As referências do capítulo 1 encontram-se ao final da dissertação.

RESUMO GERAL

Este estudo teve como objetivo avaliar os efeitos sedativos, analgésicos e cardiorrespiratórios, bem como segurança e grau de relaxamento muscular transoperatório da infusão contínua (IC) de dexmedetomidina (DEX) ou xilazina (XILA), como parte de um protocolo balanceado contendo morfina, lidocaína, cetamina e propofol em cadelas submetidas a ovariohisterectomia (OH). Foram utilizadas 39 cadelas hígidas, as quais foram distribuídas aleatoriamente em quatro grupos (n = 10 [Dex]; n = 9 [DexIC]; n = 9 [Xila]; n = 11 [XilaIC]). Os grupos Dex e DexIC receberam medicação pré-anestésica (MPA) composta de DEX (10 µg/kg) e morfina (0,5 mg/kg), ambas IM, enquanto os grupos Xila e XilaIC receberam XILA (0,3 mg/kg) e morfina (0,5 mg/kg). Todos os cães foram induzidos à anestesia com uma combinação de lidocaína (1 mg/kg/IV), cetamina (1 mg/kg/IV) e propofol (suficiente para permitir intubação endotraqueal). Após a intubação, as infusões foram iniciadas. Todos os animais receberam infusão contínua de propofol para manutenção do plano anestésico (iniciando em 0,3 mg/kg/min), lidocaína (1 mg/kg/h) e cetamina (0,6 mg/kg/h) para analgesia complementar. Os cães no grupo XilaIC também receberam infusão contínua de XILA (0,3 mg/kg/h), assim como no grupo DexIC infusão contínua de DEX (1 µg/kg/h). Os escores de sedação foram avaliados 5, 10 e 15 minutos após MPA, e o relaxamento muscular foi avaliado durante o procedimento. Os parâmetros cardiorrespiratórios (PAM, FC, FR, Temp, SpO_2 e $EtCO_2$) foram avaliados antes (BL) e durante o procedimento (em 5 momentos). A necessidade de resgate analgésico foi avaliada durante e após o procedimento, e o tempo para extubação foi registrado. Seis animais (Dex: 1; DexIC: 2; Xila: 2; XilaIC: 1) necessitaram de resgate analgésico transoperatório (fentanil 1,5 µg/kg/IV), mas nenhum no pós-operatório imediato. O grupo XilaIC (10, 4-18 min) apresentou tempo para extubação maior quando comparado aos grupos Xila (5, 1-8 min) e DexIC (6, 2-22 min). Os valores de FC foram maiores no grupo Xila quando comparados aos demais grupos. Em contraste com o grupo Dex, os valores de PAM foram maiores no grupo Xila e menores no grupo XilaIC. Houve redução nos valores de FC, FR e Temp dentro de todos os grupos, quando comparados aos valores basais. Não houve diferença significativa nos demais parâmetros avaliados. Todos os protocolos demonstraram boa sedação, analgesia, relaxamento muscular transoperatório e segurança. Portanto, todos foram considerados adequados para OH em cães. No entanto, resgate analgésico transoperatório pode ser necessário em alguns animais, mas não no período pós-operatório imediato. Os protocolos Dex e Xila podem ser mais indicados para este procedimento devido a menor depressão cardiorrespiratória como um todo, visto que a OH é considerada um estímulo nocivo de intensidade moderada.

Palavras-chave: cães; analgésicos opioides; anestesia intravenosa; analgesia; monitorização fisiológica; manejo da dor.

ABSTRACT

This study aimed to evaluate the sedative, analgesic and cardiorespiratory effects, as well as safety and transoperative muscular relaxation degree caused by dexmedetomidine (DEX) or xylazine (XYLA) in constant rate infusion (CRI), both as part of a balanced protocol containing morphine, lidocaine, ketamine and propofol in bitches undergoing ovariohysterectomy (OH). Thirty-nine healthy female dogs were included and randomly assigned to four groups (n = 10 [Dex]; n = 9 [DexCRI]; n = 9 [Xyla]; n = 11 [XylaCRI]). Dogs in Dex and DexCRI groups received a combination of morphine (0.5 mg/kg) and DEX (10 µg/kg) intramuscularly as premedication, while dogs in Xyla and XylaCRI groups received morphine (0.5 mg/kg) and xylazine (0.3 mg/kg). All dogs were induced to anesthesia with a combination of lidocaine (1 mg/kg), ketamine (1 mg/kg) and propofol (enough to allow endotracheal intubation). After intubation, the infusions started. All groups received propofol infusion for anesthesia maintenance (starting at 0.3 mg/kg/min), lidocaine (1 mg/kg/h) and ketamine (0.6 mg/kg/h) for analgesia. Dogs in DexCRI group also received DEX CRI (1 µg/kg/h), while dogs in XylaCRI group received XYLA CRI (0.3 mg/kg/h). Sedation scores were evaluated 5, 10 and 15 minutes after premedication, and transoperative muscular relaxation was assessed during the procedure. Cardiorespiratory variables (MAP, HR, RR, Temp, SpO_2 and $EtCO_2$) were assessed before (BL) and during the procedure (in 5 moments). The need for analgesic rescue was assessed during and after the surgery, and time to extubation was recorded. Six animals (Dex: 1; DexCRI: 2; Xyla: 2; XylaCRI: 1) needed transoperative analgesic rescue (fentanyl 1.5 µg/kg/IV), but none in the immediate postoperative period. XylaCRI group (10, 4-18 min) showed longer time for extubation when compared to Xyla (5, 1-8 min) and DexCRI (6, 2-22 min) groups. HR values were higher in Xyla group when compared to all other groups. In contrast to Dex group, MAP values were higher in Xyla group and lower in XylaCRI group. There was reduction in HR, RR and Temp values within all groups, when compared to baseline values. There was no significant difference in other parameters assessed. All protocols showed good sedation, analgesia, intraoperative muscular relaxation and safety. Thus, all were considered adequate for OH in dogs. Yet, analgesic rescue might be necessary in some animals during the procedure, but not in the immediate postoperative period. Dex and Xyla protocols might be preferred due to less cardiorespiratory depression overall, since OH is considered a moderate intensity nociceptive stimulus.

Keywords: dogs; analgesics, opioid; anesthesia, intravenous; analgesia; monitoring, physiologic; pain management.

CAPITULO 1

INTRODUÇÃO E CONTEXTUALIZAÇÃO

A ovariohisterectomia (OH) representa um dos procedimentos mais realizados na rotina cirúrgica de cães e gatos, sendo de extrema importância no controle populacional, visto a necessidade de reduzir o abandono de animais, a incidência de zoonoses e eutanásia (Tamanho et al., 2010).

De acordo com as diretrizes para reconhecimento, avaliação e tratamento da dor da *World Small Animal Veterinary Association* (WSAVA) (Mathews et al., 2014), a OH é classificada como um estímulo cirúrgico capaz de causar dor de intensidade moderada no período pós-operatório. O uso apenas de anti-inflamatórios e alguns opioides, como tramadol, morfina ou petidina, no período perioperatório pode não ser adequado no controle desta dor.

O manejo adequado da dor aguda perioperatória requer o uso de analgesia multimodal, por meio da utilização de diferentes técnicas analgésicas ou grupos farmacológicos com mecanismos de ação distintos (Schug, 2016). Esta abordagem terapêutica proporciona um efeito sinérgico entre os fármacos e permite o uso de doses mais baixas para se obter boa resposta terapêutica, logo, espera-se menor incidência de reações adversas (Gurney, 2012). Os grupos comumente utilizados na analgesia multimodal incluem anti-inflamatórios não esteroidais (AINEs), opioides, anestésicos locais, antagonistas de receptores N-metil-D-aspartato (NMDA) e α2-agonistas (Mathews et al., 2014).

Os opioides desempenham papel fundamental em protocolos analgésicos, sendo utilizados como parte da medicação pré-anestésica (MPA) de rotina (Epstein et al., 2015), a fim de englobar os períodos trans e pós-operatório imediato. A morfina é um opioide μ-agonista puro, exercendo seus efeitos terapêuticos ao se ligar a receptores μ no sistema nervoso central e periférico. Ao se ligar a receptores pré-sinápticos, inibe a liberação de neurotransmissores excitatórios provenientes de fibras aferentes na medula espinhal e, consequentemente, atua na modulação da dor (Mathews et al., 2014). No entanto, conforme demonstrado por Almeida et al. (2013), o uso de morfina isoladamente se mostrou ineficaz no controle da dor trans e pós-

operatória em cadelas submetidas a OH eletiva, visto que todos os animais medicados com morfina (0,5 mg/kg) por via intramuscular logo após a indução anestésica necessitaram de resgate analgésico no pós-operatório, enquanto que a associação de morfina e cetamina (2,5 mg/kg) se mostrou eficaz no controle da dor pós-operatória.

Segundo as diretrizes para manejo da dor em cães e gatos da *American Animal Hospital Association* (AAHA) (Epstein et al., 2015), sugere-se o uso pré-operatório de opioides associados a fármacos com efeitos tranquilizantes ou sedativos, como, por exemplo, os α2-agonistas. Há efeito sinérgico importante entre estas duas classes de fármacos, o que permite a utilização destes em doses mais baixas, proporcionando boa sedação e analgesia. O uso de doses reduzidas tende a minimizar os efeitos cardiovasculares e respiratórios adversos provocados por ambos os grupos.

Os efeitos analgésicos promovidos pelos α2-agonistas são dose-dependentes, e o principal mecanismo de ação ocorre por inibição da liberação de noradrenalina. Em geral, os efeitos sedativos e ansiolíticos são mediados pela ativação de receptores supraespinhais localizados no tronco cerebral, enquanto os efeitos analgésicos são mediados pela ativação de receptores localizados no corno dorsal da medula espinhal.

Os efeitos sedativos comumente observados com a administração de α2-agonistas incluem ataxia, relaxamento muscular e decúbito lateral ou esternal. Também são utilizados com o intuito de produzir relaxamento muscular e redução do requerimento de fármacos anestésicos injetáveis e inalatórios (Oleskovicz e Corrêa, 2012). É importante ressaltar que os efeitos analgésicos produzidos pelos α2-agonistas são de duração mais curta quando comparados aos seus efeitos sedativos (Berry, 2015), o que sugere que sua analgesia pode não ter o tempo de duração desejado ao longo de um procedimento cirúrgico.

Os fármacos desta classe promovem efeitos adversos significativos sob os sistemas cardiovascular e respiratório. Dentre os efeitos cardiovasculares, hipertensão transitória seguida de redução da pressão arterial (resultante de alterações na resistência vascular sistêmica [RVS]), bradicardia, redução do débito cardíaco e volume sistólico são de grande impacto durante a anestesia (Berry, 2015). De acordo com Congdon et al. (2011), a associação de atropina com dexmedetomidina (DEX) com a finalidade de prevenir a bradicardia

causada por estes fármacos não apresenta resultados satisfatórios, pois aumenta o consumo de oxigênio pelo miocárdio e a ocorrência de arritmias cardíacas importantes, contraindicando o uso desta associação. Além do mais, a hipertensão decorrente do aumento da RVS pode ser agravada com aumento da frequência cardíaca.

A redução na frequência respiratória e no volume corrente também podem ocorrer, o que pode resultar em acidose respiratória e hipóxia em alguns animais. É importante ressaltar que os efeitos adversos podem ser observados mesmo com doses pequenas de α2-agonista e, portanto, devem ser utilizados com cautela em animais debilitados (Berry, 2015).

A DEX é um α2-agonista que apresenta propriedades ansiolíticas, analgésicas e sedativas (Chen et al., 2012). Seu uso em cães e gatos foi aprovado pela União Europeia em 2002, e nos Estados Unidos em 2006, porém, tem sido relatado desde a década de 90 em cães (Zornow et al., 1990). Sendo o composto mais novo e mais específico dentro do grupo dos α2-agonistas (cerca de 1600 vezes mais seletiva para receptores α2 do que α1), a DEX é o enantiômero ativo da medetomidina, o que a torna duas vezes mais potente. Sua meia-vida de eliminação é de cerca de 30 minutos em cães, com biotransformação hepática e eliminação renal (Lin et al., 2008).

Em decorrência do seu efeito sinérgico com opioides, a combinação de DEX com metadona ou morfina prolongou a ausência de resposta a estímulos mecânicos (pinçamento digital com pinça hemostática) por pelo menos 30 minutos em estudo realizado por Cardoso et al. (2014). Em outro estudo, ao comparar a DEX com a xilazina (XILA) na medicação pré-anestésica em cães submetidos a diversos procedimentos cirúrgicos não especificados, foi demonstrado que a qualidade na manutenção do plano anestésico foi discretamente superior com a DEX, com redução mais significativa das doses de propofol utilizadas na indução e manutenção do paciente, bem como menor depressão respiratória. No entanto, ambos os fármacos foram considerados adequados para os diversos procedimentos cirúrgicos em que foram utilizados (Jena et al., 2014).

Quando há necessidade de prolongar e potencializar os efeitos analgésicos, a DEX pode ser utilizada em infusão contínua. Segundo o estudo de Lervik et al. (2012), a DEX administrada na dose de 1 µg/kg, seguida de

infusão contínua na taxa de 1 µg/kg/h em cães submetidos a anestesia geral com isoflurano, causou efeitos antinociceptivos a estímulos elétricos e apresentou potencial para prevenir o fenômeno *wind up*, o qual ocorre devido à sensibilização central após estímulo contínuo de fibras nociceptivas e desempenha um papel fundamental na consolidação da dor crônica.

Nas campanhas de controle populacional se trabalha com grandes volumes de animais errantes e de proprietários carentes e, portanto, sempre se busca a redução de custos na realização dos procedimentos. Por este motivo, ainda se utiliza a XILA em grande escala em países em desenvolvimento. No entanto, poucos estudos recentes relatam protocolos voltados para campanhas (Tamanho et al., 2010; Barletta et al., 2011; Mascarenhas et al., 2015; Degórska et al., 2017).

A XILA vem sendo utilizada na medicina veterinária desde a década de 60 (Clarke e Hall, 1969), sendo um dos primeiros α2-agonistas sintetizados. Contudo, a literatura é escassa a respeito do uso de XILA em infusão contínua em cães, tendo poucos estudos existentes até a presente data (Benson et al., 1985; Tranquilli et al., 1988; Silva et al., 2007; Ibrahim, 2017). Por outro lado, seu uso em equinos está bem estabelecido e continua sendo estudado até o presente momento (Aarnes et al., 2018; Sage et al., 2018; Hopster et al., 2017), sendo comumente utilizada em associação com cetamina e guaiafenesina (McCarty et al., 1990).

Ibrahim (2017) estudou três diferentes associações de XILA e cetamina em infusão contínua em cães, e observou que a taxa de 1 mg/kg/h de XILA, quando utilizada em associação a 10 mg/kg/h de cetamina, proporcionou plano anestésico-cirúrgico mais adequado, com alterações mínimas nos parâmetros vitais avaliados.

Além do mais, infusões contínuas de lidocaína e cetamina tem sido amplamente utilizadas na medicina veterinária para garantir planos analgésicos mais eficazes. Quando combinados, estes fármacos agem em diferentes receptores presentes nas vias da dor (Travagin et al., 2017; Cerejo et al., 2013). A lidocaína é um anestésico local comumente utilizado para bloqueio local da dor, podendo também ser utilizada pela via intravenosa. Este fármaco age na superfície interna do canal de sódio, inibindo a transmissão do potencial de ação pelo axônio, o que leva à estabilização da membrana celular em

estado de repouso (Travagin et al., 2017). Já a cetamina é um antagonista de receptor NMDA. Este receptor, quando ativado pelo neurotransmissor excitatório glutamato, desempenha um papel fundamental no desenvolvimento da sensibilização central (Babos et al., 2013). Portanto, outro benefício em combinar estes fármacos consiste em prevenir o desenvolvimento de sensibilização central durante intervenções cirúrgicas (Muir e Woolf, 2001).

Logo, levantou-se a hipótese de que o uso de α2-agonistas como parte destes protocolos balanceados promoveria sedação moderada a intensa, além de proporcionar boa qualidade analgésica. No entanto, o efeito analgésico esperado é de curta duração após dose única e foi suposto que seu uso em infusão contínua seria mais adequado do que quando utilizados apenas como medicação pré-anestésica em cadelas submetidas a OH.

O objetivo deste estudo consistiu em avaliar os efeitos sedativos, analgésicos e cardiorrespiratórios, bem como segurança e grau de relaxamento muscular transoperatório da DEX ou XILA, com ou sem infusão contínua, ambas como parte de um protocolo balanceado contendo morfina, lidocaína, cetamina e propofol em cadelas hígidas submetidas a OH.

CAPITULO 2

(Artigo científico submetido para publicação no periódico Journal of the American Veterinary Medical Association – JAVMA)

Dexmedetomidine or xylazine infusion as part of balanced protocols for bitches in spay-neuter programs

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Abstract

OBJECTIVE – To evaluate sedative, analgesic and cardiorespiratory effects, as well as safety and transoperative muscular relaxation degree of dexmedetomidine (DEX) or xylazine (XYLA) in constant rate infusion (CRI), as part of balanced protocols in bitches undergoing ovariohysterectomy (OH) in spay-neuter programs.

DESIGN – Prospective, randomized, blind study.

ANIMALS – 39 client-owned healthy sexually intact female dogs.

PROCEDURES – Dex (n = 10) and DexCRI (n = 9) groups received a combination of morphine (0.5 mg/kg [0.23 mg/lb]) and DEX (10 µg/kg [4.5 µg/lb]) intramuscularly as premedication, while Xyla (n = 9) and XylaCRI (n = 11) groups morphine (0.5 mg/kg [0.23 mg/lb]) and XYLA (0.3 mg/kg [0.14 mg/lb]). All dogs were induced to anesthesia with a combination of lidocaine (1 mg/kg [0.45 mg/lb]), ketamine (1 mg/kg [0.45 mg/lb]) and propofol (dose-effect). All dogs received propofol for anesthesia maintenance (starting at 0.3 mg/kg/min [0.14 mg/lb/min]), lidocaine (1 mg/kg/h [0.45 mg/lb/h]) and ketamine (0.6 mg/kg/h [0.27 mg/lb/h]) for analgesia. DexCRI group also received DEX CRI (1 µg/kg/h [0.45 µg/lb/h]), while XylaCRI group XYLA CRI (0.3 mg/kg/h [0.14 mg/lb/h]). Sedation scores were evaluated 5, 10 and 15 minutes after premedication. Cardiorespiratory variables were assessed. The need for analgesic rescue was assessed during and after the surgery, and time to extubation was recorded.

RESULTS – Six animals (Dex: 1; DexCRI: 2; Xyla: 2; XylaCRI: 1) received fentanyl during surgery, but no animals needed rescue analgesics in the immediate postoperative period. There was significant difference in sedation scores at 5 min, MAP, HR and time to extubation between groups, with no significant difference in all other parameters evaluated.

CONCLUSIONS AND CLINICAL RELEVANCE – All protocols showed good sedation, analgesia, intraoperative muscular relaxation and safety. Thus, all were considered adequate for OH in dogs. Yet, analgesic rescue might be necessary in some animals during the procedure, but not postoperatively. Dex and Xyla protocols might be preferred due to less cardiorespiratory depression overall.

Key words: Anesthesiology-small animal; pain; anesthetic agents.

Abbreviations list

BRL – brazilian real

CRI – continuous rate infusion

DEX – dexmedetomidine

EtCO2 – end-tidal carbon dioxide (mmHg)

HR – heart rate (bpm)

MAP – mean arterial pressure (mmHg)

OH – ovariohysterectomy

RR – respiratory rate (bpm)

SpO2 – peripheral capillary oxygen saturation (%)

Temp – body temperature (˚C)

XYLA – xylazine

Ovariohysterectomy is one of the most common surgeries performed in dogs and cats, playing an important role in reducing animal abandonment, zoonosis transmissions and euthanasia rates[1]. Classified as a moderate intensity pain stimulus, OH requires a combination of drugs acting in different receptors in pain pathways in order to provide a better quality analgesia overall[2].

Besides prioritizing analgesia quality, when shelter medicine and spay-neuter programs are taken into account, some issues must be anticipated by veterinarians. These include a large number of patients of different ages and weights, along with limited finances and diagnostic capabilities prior to surgery[3]. In this scenario, thorough physical examination and detailed medical history are imperative in order to increase perioperative safety[4].

In Brazil, shelter medicine is customarily carried out by non-governmental organizations or universities in partnership with town halls, for which economically viable protocols are a necessity[1]. Unfortunately, the use of medical care guidelines for spay-neuter programs[4] is not a reality, as most programs work on a very limited budget. Therefore, practical and low-cost balanced protocols with good analgesia are usually preferred. Opioids are widely used as a first choice while treating perioperative pain. There is important synergy between opioids and α2-agonists, allowing the use of lower doses to obtain good sedation and analgesia, while reducing cardiovascular effects as well[5].

DEX is a highly selective α2-agonist, while XYLA is one of the first synthetized and the least selective α2-agonist drug available, both being widely employed in veterinary medicine for their anxiolytic, analgesic and sedative effects[6]. Despite being used in veterinary medicine for over five decades[7], literature is scarce regarding XYLA's use as CRI in dogs, with few existing studies to this date[8-11].

Among α2-agonists' most commonly observed cardiovascular effects, transient increase in blood pressure followed by a decrease (resultant from systemic vascular resistance changes), bradycardia and cardiac output reduction are of great impact during anesthesia. Moreover, respiratory rate and tidal volume decrease are other common adverse effects, which may result in respiratory acidosis and hypoxia in some animals[12].

Lidocaine and ketamine CRIs have been extensively used in veterinary medicine to ensure effective analgesia. When combined, these drugs act on different receptors present in the pain pathways[13,14]. Lidocaine is a local anesthetic commonly used for local blockage of pain, but can also be used IV. Lidocaine acts on the internal surface of the sodium channel, preventing the transmission of the action potential by the axon, leading to stabilization in a standby state[13]. Ketamine is a N-methyl-D-aspartate antagonist. This receptor, when activated by the excitatory neurotransmitter glutamate, plays a crucial role in the development of central sensitization[15]. Thus, another benefit of combining these drugs is to prevent the development of central sensitization during surgical intervention[16].

Therefore, it was hypothesized that DEX or XYLA CRI would provide better analgesia and muscular relaxation when compared to their use as a single dose as premedication in dogs undergoing OH, as part of a balanced protocol containing morphine (single dose), lidocaine-ketamine CRI and propofol maintenance.

MATERIALS AND METHODS

Animals – Thirty-nine client-owned bitches submitted to OH participated in this study. The dogs were between 5 and 108 months old (median 24 months), with body weight between 1.8 and 51 kg (median 10.4 kg; 3.97 to 112.44 lbs [median 22.93 lbs]). Inclusion criteria comprised of healthy sexually intact female dogs, proven by physical examination, anamnesis and laboratory blood tests (hematological and biochemical), aging between 5 months and 9 years, of any breed and any weight.

Owner consent was obtained for inclusion of each of the dogs in the study, which was approved by the Animal Usage Ethics Committee (protocol 01187).

Experimental procedure – The study was conducted as a prospective, randomized, blind design. The 39 dogs were randomly allocated into one of the four treatment groups (n = 10 for group Dex; n = 9 for DexCRI; n = 9 for Xyla; n = 11 for XylaCRI).

Food was withheld for 8 hours, and water for 2 hours before anesthesia. After admission of the animals in preparation room, a complete physical exam was performed. The heart rate (HR, bpm), respiratory rate (RR, bpm), rectal temperature (Temp, ˚C), and mean arterial blood pressure (MAP, mmHg), measured by an oscillometric device[a], were used as baseline (BL) values for further comparisons.

Dogs in Dex and DexCRI groups received a combination of morphine (0.5 mg/kg [0.23 mg/lb]) and DEX (10 µg/kg [4.5 µg/lb]) as premedication, administered intramuscularly in the semitendinous as a single injection, while dogs in Xyla and XylaCRI groups received morphine (0.5 mg/kg [0.23 mg/lb]) and XYLA (0.3 mg/kg [0.14 mg/lb]).

In sequence, the dogs were prepared for surgical procedure. A catheter of appropriate size was placed in the cephalic vein, in order to establish an administration route for fluids and CRI protocols. Ringer lactate was infused at a rate of 5 mL/kg/h (2.27 mL/lb/h), controlled by a peristaltic infusion pump[b]. The patients were then transported into the operating room, where induction to anesthesia occurred with a combination of lidocaine (1 mg/kg [0.45 µg/lb]), ketamine (1 mg/kg [0.45 µg/lb]) and propofol (enough to allow endotracheal intubation; the doses needed for each animal were recorded) in all groups. The animals were intubated with endotracheal tubes of appropriate size and kept in oxygen 100% during the procedure. A non-rebreathing Magill circuit was used for dogs under 10 kg, while dogs above 10 kg were connected to a rebreathing circular system, both attached to an anesthetic machine[c] with air flow adjusted to 100 ml/kg (45 ml/lb). After intubation, the infusions (propofol and analgesics) started and were kept until the end of the surgery (END moment), with the aid of two syringe pumps[d,e], in

which the analgesic infusions were assembled to a 0.5 ml/kg/h (0.23 ml/lb/h) rate for all groups. Therefore, all groups received the same volume. There was an interval of at least 15 minutes before the first surgical incision (INI moment), to ensure adequate analgesia was being provided by the infusions. All dogs received propofol infusion for anesthesia maintenance, starting at 0.3 mg/kg/min (0.14 mg/lb/min) and adjusted according to anesthetic depth (absence of palpebral reflex, jaw tone and pedal reflex). Total volume of propofol infused (mL) and the rates (mg/kg/min) used along the surgery were recorded. Lidocaine (1 mg/kg/h [0.45 mg/lb/h]) and ketamine (0.6 mg/kg/h [0.27 mg/lb/h]) CRI were also maintained for complementary analgesia in all groups. Dogs in DexCRI group also received DEX CRI (1 µg/kg/h [0.45 µg/lb/h]), while dogs in XylaCRI group received XYLA CRI (0.3 mg/kg/h [0.14 mg/lb/h]). A catheter of adequate size was placed transcutaneously in the femoral artery for continuous monitoring of invasive blood pressure, and the pressure transducer was zeroed to ambient atmospheric pressure and centered at the level of the right atrium.

Cardiorespiratory variables were assessed. Fentanyl (1.5 µg/kg [0.68 µg/lb], IV) was given when analgesia was considered inadequate during the procedure (MAP increases over 30% when compared to previous value, correlated with changes in respiratory pattern, surgical stimuli and adequate anesthetic plan), and morphine (0.3 mg/kg [0.14 mg/lb], IM) was given when analgesia was considered inadequate in the immediate postoperative period, after patient recovery and pain assessment (pain scores above 13 points, using the University of Melbourne Pain Scale[17]). If $EtCO_2$ values were above 60 mmHg, assisted ventilation was initiated in order to maintain normocapnia. Time to extubation was recorded, from the END until cough reflex or swallowing was evident. Total time of anesthesia (from induction until extubation moment) and surgery (from INI to END moment) were also recorded.

Total cost with medications (premedication, induction, maintenance and analgesic infusions) were estimated for all groups.

Patient monitoring – During the surgery, the following parameters were registered every 5 minutes: HR (bpm), RR (bpm), MAP (mmHg), SpO_2 (%), Temp (^{0} C) and $EtCO_2$ (mmHg). MAP values were obtained with an invasive blood pressure (IBP) system connected to a multiparameter monitor[f]. This same monitor was used to record the other aforementioned parameters. ECG was evaluated continuously in order to detect important arrhythmias, by using DII derivation of another multiparameter monitor[g]. Important surgical moments were recorded for each dog: start of surgery (INI), ligature of the left and right ovarian pedicles (LO and RO, respectively), ligature of the cervix (C) and end of surgery (END). In order to maintain adequate anesthetic depth, parameters related to anesthetic plan were also observed: palpebral reflex (absent or present), ocular globe position, and pupil diameter (miosis or mydriasis).

Scores evaluated – Degree of sedation was evaluated 5, 10 and 15 minutes after administration of premedication by an adapted score system[18] (Appendix). Dex and DexCRI groups were considered as one, as well as Xyla and XylaCRI groups (same premedications).

Intraoperative muscular relaxation degree was evaluated in accordance with the surgeon by a simple score system, from 0 to 3, where 0 would be poor relaxation (no muscular relaxation, difficult to pull the pedicle), 1 regular (poor muscular relaxation, less resistance to pull the pedicle), 2 good (good muscular relaxation, no difficulty to pull the pedicle, yet not totally relaxed), and 3 optimal (excellent muscular relaxation, pedicle totally relaxed).

After patient recovery (return of consciousness, normal reflexes and sternal recumbency), pain was evaluated with the University of Melbourne Pain Scale[17]

(supplementary material). Animals with scores above 13 points received morphine 0.3 mg/kg (0.14 mg/lb) intramuscularly as analgesic rescue. After this evaluation, all animals received meloxicam 0.2 mg/kg (0.09 mg/lb) intramuscularly.

Statistical analysis – For statistical analysis, Shapiro-Wilk normality test and Levene's test for equality of variances were applied. Variables with normal distribution (MAP, $EtCO_2$, Temp, total volume of propofol infused) were analyzed by ANOVA test, followed by Bonferroni's test, which reduces error type II, once homoscedasticity was not observed in some situations. In variables with significant difference between groups, Student's T-test was performed for unpaired samples, and paired Student's T-test was used to compare moments within the same group. Results are expressed as mean and standard deviation. For nonparametric data and without normal distribution (HR, RR, SpO_2, propofol rates, propofol induction doses, time to extubation, total time for surgery and anesthesia, cost with medications, sedation, transoperative and postoperative pain scores), Kruskal-Wallis test was used. In variables with significant difference between groups, Mann-Whitney test was performed for unpaired samples. Mann-Whitney Wilcoxon signed-rank test was used to compare moments within the same group. These results are expressed as median and range. Chi-square test was performed in order to compare analgesic rescues, occurrence of emesis, apnea and the need for assisted ventilation between groups. Significance level adopted was 5% ($\alpha<0.05$). All tests were performed with the aid of a commercially available software[h].

RESULTS

Seventeen animals (43.59%) were mixed-breed dogs, and the most common breeds were Lhasa Apso (7.69%) and Border Collie (7.69%). Other breeds participating in the

study were Pinscher, Chow Chow, Yorkshire, Shih Tzu, Blue Heeler, Poodle, Golden Retriever, Labrador, Pit Bull, Cane Corso, Maltese and Dachshund.

Six animals (Dex: 1 [10%]; DexCRI: 2 [22.22%]; Xyla: 2 [22.22%]; XylaCRI: 1 [9.09%]) needed analgesic rescue during surgery, however, there was no significant difference ($p = 0.75$) between groups. None of the dogs in this study needed analgesic rescue in the immediate post-operative period.

Out of the 39 animals that participated in this study, twenty-four (61.54%) had emesis after premedication, being eleven (57.89%) out of nineteen with DEX and morphine, and thirteen (65%) out of twenty with XYLA and morphine.

Since Dex and DexCRI groups received the same premedications and induction protocols, they were considered as one group (Dex) for propofol doses used for anesthetic induction, and the same was applied to Xyla and XylaCRI groups (Xyla). There was no significant difference ($p = 0.11$) in propofol doses used for anesthetic induction between groups (Dex: 1.43, 0-8.8 mg/kg [0.65, 0-3.99 mg/lb]; Xyla: 1.81, 0.19-4.13 mg/kg [0.82, 0.09-1.87 mg/lb]). There was also no significant difference ($p = 0.15$) in total propofol infused between groups (Dex: 14.14 ± 7.24 mL; DexCRI: 14.81 ± 8.85 mL; Xyla: 21.84 ± 8.62 mL; XylaCRI: 19.83 ± 9.8 mL), as well as in propofol rates used (Dex: 0.2, 0.05-0.9 mg/kg/min [0.09, 0.02-0.41 mg/lb/min]; DexCRI: 0.3, 0.15-1.0 mg/kg/min [0.14, 0.07-0.45 mg/lb/min]; Xyla: 0.4, 0.1-0.6 [0.18, 0.045-0.27 mg/lb/min]; XylaCRI: 0.3, 0-0.6 [0.14, 0-0.27 mg/lb/min][medians, and range between the five moments assessed]).

XylaCRI group showed significantly higher time to extubation (10, 4-18 min) when compared to Xyla (5, 1-8 min; $p = 0.009$) and DexCRI (6, 2-22 min; $p = 0.047$) groups, but not to Dex (5, 2-25; $p = 0.056$) group.

There was no significant difference in total time of anesthesia (Dex: 66, 52-83 min; DexCRI: 55, 42-108 min; Xyla: 54, 47-112 min; XylaCRI: 60, 45-96 min; $p = 0.07$) and time of surgery (Dex: 36, 27-65 min; DexCRI: 25, 19-85 min; Xyla: 30, 22-80 min; XylaCRI: 35, 18-65 min; $p = 0.18$) between groups.

Cardiorespiratory parameters monitored during the surgeries are presented in Tables 1 (normally distributed) and 2 (non-normally distributed). Regarding these parameters, there was no significant difference ($p > 0.05$) in SpO_2 and $EtCO_2$ values between groups, or between different moments within each group. HR was significantly higher in Xyla group when compared to all other groups in most moments (LO, RO, C and END). There was significant reduction ($p < 0.05$) in HR values from BL moment (Dex: 116, 71-160 bpm; XylaCRI: 112, 76-212 bpm) to all other moments in Dex (INI: 75.5, 46-128 bpm; LO: 85.5, 45-120 bpm; RO: 77.5, 60-135 bpm; C: 80, 47-142 bpm; END: 79, 43-150 bpm) and XylaCRI (INI: 79, 55-107 bpm; LO: 82, 43-108 bpm; RO: 82, 53-98 bpm; C: 82, 51-94 bpm; END: 81, 46-100 bpm) groups, but without differing significantly within DexCRI and Xyla groups.

When compared to Dex group (LO: 108.9 ± 13.96 mmHg; END: 104.5 ± 14.02 mmHg), MAP values were significantly higher ($p = 0.032$) in Xyla group (124.67 ± 13.81 mmHg) in LO moment, and significantly lower ($p = 0.029$) in XylaCRI group (87.19 ± 13.31 mmHg) in END moment. Also, there was significant difference ($p < 0.05$) in different moments within each group, with all groups showing lower values at INI and END moments.

Overall, there was reduction in RR rates in all moments within all groups when compared to BL values. There was no significant difference ($p > 0.05$) in RR values between groups in all different moments assessed. However, there was significant reduction ($p < 0.05$) in RR values for Dex group, from BL moment (33.5, 16-140 bpm)

to INI (13, 9-35 bpm; p = 0.033), RO (19.5, 8-44 bpm; p = 0.047) and C (14, 0-30 bpm; p = 0.019) moments and in XylaCRI group, from BL (28, 16-120 bpm) to INI (12, 7-34 bpm), RO (17, 6-44 bpm) and END (14, 8-34 bpm) moments, but with no significant difference in DexCRI and Xyla groups.

A reduction in Temp values was observed in all groups. However, it was significant ($p < 0.05$) in DexCRI, Xyla and XylaCRI groups. There was no significant difference ($p > 0.05$) in Temp values between groups, or in different moments for Dex group.

Two animals (Dex: 1; Xyla: 1) displayed second degreee atrioventricular block. Sinus arrhythmia was observed in five dogs (50%) in Dex group, three dogs (33.33%) in DexCRI group, one dog in Xyla group (11.11%), and seven dogs (63.64%) in XylaCRI group. Assisted ventilation was needed for three animals (30%) in Dex group, six animals (66.67%) in DexCRI group, two animals (22.22%) in Xyla group, and four animals (36.37%) in XylaCRI, for which there was no significant difference (p = 0.23) between groups. Furthermore, there was no significant difference (p = 0.33) in apnea occurrence between groups (Dex: 2 animals [20%]; DexCRI: 3 animals [33.33%]; Xyla: 0; XylaCRI: 2 [18.18%]).

In relation to assessed scores, sedation scores were significantly higher (p = 0.027) in Dex groups (3, 0-7) when compared to Xyla groups (1, 0-5) 5 min after premedication. There was also significant difference in moments within groups (Figure 1). There was no significant difference in transoperative muscular relaxation scores (Dex: 3, 2-3; DexCRI: 2, 1-3; Xyla: 2, 1-3; XylaCRI: 3, 1-3; p = 0.20) and postoperative pain scores (Dex: 3, 0-8; DexCRI: 4, 0-9; Xyla: 5, 2-11; XylaCRI: 4, 1-8; p = 0.14) between groups (Table 3).

Total costs with medications were 25.08 ± 8.85 BRL (brazilian real) (6.42 ± 2.26 US$) for Dex group, 23.72 ± 14.11 BRL (6.07 ± 3.61 US$) for DexCRI group, 16.44 ± 6.24

BRL (4.21 ± 1.60 US$) for Xyla group and 18.55 ± 10.33 BRL (4.75 ± 2.64 US$) for XylaCRI group. There was no significant difference (p = 0.80) between groups.

DISCUSSION

This study evaluated balanced anesthesia protocols with DEX or XYLA CRI for bitches submitted to OH, protocols until then not reported in scientific medical literature.

Considering α2-agonists' short time of action, it was expected that Dex and Xyla protocols could be inadequate to perform the surgeries. However, we observed no difference in relation to analgesia and propofol requirements during anesthesia. According to an earlier study[19], the combination of DEX and morphine prolonged the absence to noxious stimuli for over 30 minutes. In the present study, we believe the synergistic effect of this association may have provided long lasting analgesia in the groups without α2-agonists CRI, seeing how few animals needed analgesic rescue during surgery. Nonetheless, all groups also received lidocaine and ketamine CRI, that may have contributed to a good quality analgesia in these animals.

Few studies report the use of XYLA as a CRI in dogs[8-11], which can be associated to a protocol in order to increase its analgesic, sedative and transoperative muscular relaxation effects. Moreover, the advantages of incorporating an α2-agonist in the anesthetic protocol also include general anesthetic reduction and reversibility[20]. In bitches undergoing OH, in which the pain stimulus is of moderate intensity, α2-agonists CRI might be unnecessary as part of a protocol containing morphine, lidocaine and ketamine as adjunctive analgesics. However, more studies are required in order to evaluate their use in more painful and invasive procedures.

Out of the six animals that received analgesic rescue, five were small dogs (a Yorkshire, a Poodle, a Lhasa Apso and two mongrels). In a previous study[21], there was difference

in pain sensitivity provoked by thermal stimuli among the assessed breeds. However, the authors report that there is little information regarding the physiological differences relevant in understanding sensitivity variations between different dog breeds. In the present study, clinical observations suggest that some small breeds, like Poodle, Lhasa Apso and Yorkshire, tend to show less tolerance to pain. Besides, the need for analgesic rescue might have occurred due to higher metabolic rates in these animals, which reduces drug half-life, since most of them were small (under 8 kg [17.64 lb]) and young (under 4 years old) dogs.

Emesis occurrence was similar with DEX and XYLA. Emesis occurred in 11 animals (57.89%) within Dex groups, differing from another study[19] that used the same doses of DEX and morphine, in which the occurrence was 16.67% (1/6). Another study[22] using only DEX in the same dose found the prevalence of emesis was also 16.67% (1/6). An earlier study[23] reported a frequency of emesis of 20% in dogs premedicated with XYLA, which is not in accordance with our results. Emesis occurred in 13 animals (65%), which also differs from another study[24] where the incidence was 17%. However, the results obtained are in accordance to another study[22], in which a frequency of 83.33% (5/6) was observed with XYLA (1 mg/kg [0.45 mg/lb], IM) premedication. Emesis is likely a result of central α2 adrenergic receptor stimulation[25]. In addition to that, low doses of morphine tend to produce an emetic effect through stimulation of dopamine receptors in the chemoreceptor trigger zone, which occurred in 16.67% (1/6) in one study with dogs receiving morphine 0.5 mg/kg (0.23 mg/lb) intravenously, 15 minutes after being premedicated with acepromazine, which has known antiemetic effects[24]. It was supposed that the population observed in this study might have greater sensitivity to nausea and emesis. Fourteen breeds (56.41%) participated in this study, whilst in the compared studies, most dogs were mongrels.

The α2-agonists have marked anesthetic sparing effects both for the induction and maintenance of anesthesia. Premedication with XYLA and DEX was found to decrease anesthetic requirements during anesthesia with propofol. There was no difference in the induction doses of propofol between Dex and Xyla groups, which is in accordance to an earlier study[26] that compared DEX in the same dose as our study to XYLA in a higher dose (0.5 mg/kg [x mg/lb]), both IV. However, induction doses of propofol found in our study were lower than the reported induction dose of 2.72 ± 0.15 mg/kg (1.23 ± 0.07 mg/lb) for DEX, and 3.17 ± 0.21 mg/kg (1.44 ± 0.1 mg/lb) for XYLA[26], which was expected, since animals in the present study also received morphine as premedication, and lidocaine-ketamine as coinduction agents.

There was also no difference in propofol rates used for anesthesia maintenance between groups. We expected the groups with α2-agonist infusions to achieve lower propofol rates, and this probably did not occur due to great variability in dogs' size and age in this study, since a tendency in smaller and younger dogs needing higher rates of propofol for anesthetic maintenance was observed. This could be explained due to differences in metabolic rates provided by factors such as age, size and breed in these dogs[27].

Another study[19] using the same doses of morphine and DEX as premedication, reported intense sedation scores, which differs from the present study. However, different sedation score scales were used, what limits further comparing these scores.

In our study, the dose of DEX was based on animal weight rather than body surface area (BSA). Thus, lighter dogs may have been administered a relatively smaller dose compared with a dose calculated using BSA, what may have contributed to the wide variability in sedation scores obtained. However, doses based on animal body weight were preferred for being practical on a spay-neuter program setting.

Sedation scores obtained 5 minutes after premedication were higher in Dex groups when compared to Xyla groups. This is in accordance to an earlier study[26], where attenuation of all reflexes was quicker in animals receiving DEX when compared to XYLA, both IV.

Regarding time to extubation between groups, we suggest that the DEX rate chosen (1 µg/kg/h [0.45 µg/lb/h]) did not extend recovery time in this study, but the XYLA rate chosen did (0.3 mg/kg/h [0.14 mg/lb/h]), since XylaCRI group showed higher time to extubation than all other groups. To the author's knowledge, only one other study evaluated the influence of XYLA on recovery time after propofol anesthesia[28], and findings in our study are in accordance, since these authors reported that XYLA (0.8 mg/kg [0.36 mg/lb], IM) prolonged propofol (3 mg/kg [1.36 mg/lb]) anesthesia after a single IV injection in dogs. However, we evaluated XYLA and propofol as infusions, while the aforementioned study evaluated these drugs as single doses.

According to another study[29], which compared three different rates of DEX (1, 2 and 3 µg/kg/h [0.45, 0.9 and 1.36 mg/lb/h]) in dogs submitted to several different surgical procedures, the rate of 1 µg/kg/h (0.45 mg/lb/h) displayed the most favorable results, since this group showed significantly higher HR values when compared to the rate of 2 µg/kg/h (0.9 mg/lb/h), and there was a higher incidence of second degree atrioventricular block with the rate of 3 µg/kg/h (1.36 mg/lb/h). This study[29] also performed serial lactate measurements, and results indicate there was no tissue hypoperfusion with the use of DEX CRI in all three rates evaluated. However, the chosen DEX rate (1 µg/kg/h [0.45 mg/lb/h]) might have been low, since there was no difference in propofol infusion rates, as well as transoperative relaxation scores, postoperative pain scores and cardiorespiratory parameters assessed (MAP, HR, RR, Temp, SpO_2 and $EtCO_2$), when compared to control group (without infusion).

Literature is scarce regarding infusion rates of XYLA in dogs. Another author[11] studied four different rates of the association between XYLA and ketamine in CRI, and observed that the rate of 1 mg/kg/h (0.45 mg/lb/h) of XYLA, when used in association with ketamine (10 mg/kg/h [4.53 mg/lb/h]), provided adequate anesthetic depth, with minimal changes in vital parameters assessed. Nonetheless, we supposed a lower rate of XYLA (0.3 mg/kg/h [0.14 mg/lb/h]) would be more adequate as part of a balanced protocol due to α2-agonists' great synergy with opioids, and the addition of lidocaine-ketamine CRI and propofol maintenance. Nonetheless, the XYLA rate chosen as part of this balanced protocol might have been high, seeing how MAP values were lower for XylaCRI group, despite being mostly maintained within normal ranges for dogs.

A decrease in HR occurred in all groups, which was in accordance with previous studies using α2-agonists[26,30-32]. DEX produces a dose-dependent reduction in HR for at least 2 hours in more than 50% of dogs[33]. Studies with α2-agonists suggest that this effect occurs largely due to increased systemic vascular resistance caused by stimulation of post-synaptic α2-receptors located in peripheral vascular smooth muscle. This can be associated with increased vagal tone and decreased heart rate[20,34]. Therefore, the resulting transient hypertension induces a baroreceptor-mediated reflex bradycardia, which is exacerbated by stimulation of pre-synaptic α2-receptors in the brainstem[20].

According to another study[19] in which the association of DEX and morphine was used in the same doses as the present study, HR values decreased significantly when compared to baseline values. Another study[35] reported a reduction of 21% in HR, with bradycardia occurring in 45% of dogs by using a combination of morphine (0.5 mg/kg [0.23 mg/lb]) and acepromazine (0.02 mg/kg [0.009 mg/lb]). Findings in our study are in accordance with both aforementioned studies.

The high baseline (BL moment) arterial pressures could be due to a lack of acclimation of the animals or a result of using an indirect technique (oscillometric device) to measure arterial blood pressure, with its inherent inaccuracies, especially with awake and moving animals[19].

MAP values are lower in INI moment than in all other moments in all groups. Arterial blood pressure increased in both Dex and DexCRI groups in LO and RO moments, and in C moment within Dex group, for these are moments of ovary and cervix traction and resection, respectively, which are considered moments of higher surgical nociceptive stimuli[36].

Although MAP values were lower in XylaCRI group, this was expected. However, MAP values were maintained within normal ranges for the species evaluated in 90.91% (10/11) of dogs. Hypotension occurred in one dog in XylaCRI group (a 9-year-old Cane Corso, weighing 51 kg [112.44 lb]), which was rapidly reversed with ephedrine 0.1 mg/kg (0.045 mg/lb) intravenously. This patient displayed predisposing factors such as giant breed and senility, that likely contributed to the occurrence of hypotension, as well as apnea and sinus arrhythmia.

The depression in RR observed after administration of preanesthetics (decrease from the BL to the INI moment) might be due to direct depression of the respiratory centers in the brain[37]. Induction of anesthesia with propofol also caused a decrease in RR that was in accordance to earlier studies in dogs[26,38,39]. Moreover, respiratory depression and apnea, being the most commonly reported adverse effects of propofol anesthesia, were proportional to rate of infusion of propofol in these same studies, which was not observed in the present study due to the great variability in dogs' weight range and breeds.

However, the administration of α2-agonists decreases the RR in dogs without causing an increase in PaCO[33,40], but these agents can decrease the response to hypercapnia[41]. This, added to RR depression provided by propofol, may have contributed to the fact that some animals from all groups in our study had higher values of $EtCO_2$ and fifteen even needed assisted ventilation.

Most α2-agonists, especially XYLA, sensitize the myocardium for adrenaline induced arrhythmias[9]. However, the abnormal cardiac rhythms most frequently observed in this study (sinus arrhythmia and second degree AV blocks) can be attributed to the decreased HR induced by α2-agonists and opioids, and are not considered to be life-threatening[42].

Six animals needed assisted ventilation in DexCRI group, while in Dex group, only three. In the same way, two animals needed assisted ventilation in Xyla group, compared to four in XylaCRI group. Nonetheless, Chi-square test showed no difference between groups. We suppose greater central nervous system depression might have occurred in groups with α2-agonists infusion, and consequently greater muscular relaxation and, therefore, exacerbated respiratory depression.

As a limitation of this study, the heterogeneous population (different ages, breeds and dog sizes) may have influenced some results, since there was a great variability in sedation scores, as well as propofol maintenance rates. However, this was preferred in order to simulate a real situation occurring in spay-neuter programs[3].

Results in the present study indicate that the association of DEX or XYLA and morphine, with or without these α2-agonists' CRI, associated to lidocaine-ketamine CRI and propofol maintenance, are effective and safe protocols to perform OH on healthy dogs, rejecting the initial hypothesis that the groups with α2-agonists CRI in the chosen doses would provide greater transoperative relaxation and superior analgesia when

compared to the groups without these drugs' infusion. However, some small dogs (body weight < 10 kg [4.5 lb]) may need higher α2-agonists rates due to metabolic differences and possibly greater sensitivity to pain, and the protocol containing DEX CRI could be a more adequate choice for these animals. Nonetheless, it is important to emphasize that the excessive use of analgesics, especially α2-agonists, results in greater cardiorespiratory depression and may increase recovery time in these patients. Since OH is classified as a moderate painful stimulus, the protocols in Dex and Xyla groups provided adequate analgesia in the animals in this study. To that end, it may be beneficial to restrict α2-agonists CRI for OH in dogs.

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FOOTNOTES

a. Contec 08A Vet oscillometric blood pressure monitor
b. Dunbar eB12 peristaltic pump
c. HB Conquest 3000 anesthetic machine
d. RZ Vet RS700Vet syringe pump
e. AP-500 IV syringe pump
f. Lutech Datalys V5 multiparametric veterinary monitor
g. Dixtal DX2021 multiparametric monitor

h. STATGRAPHICS Centurion XVI version 16.1.1 for Windows, StatPoint Technologies Inc., Warrenton, VA, USA

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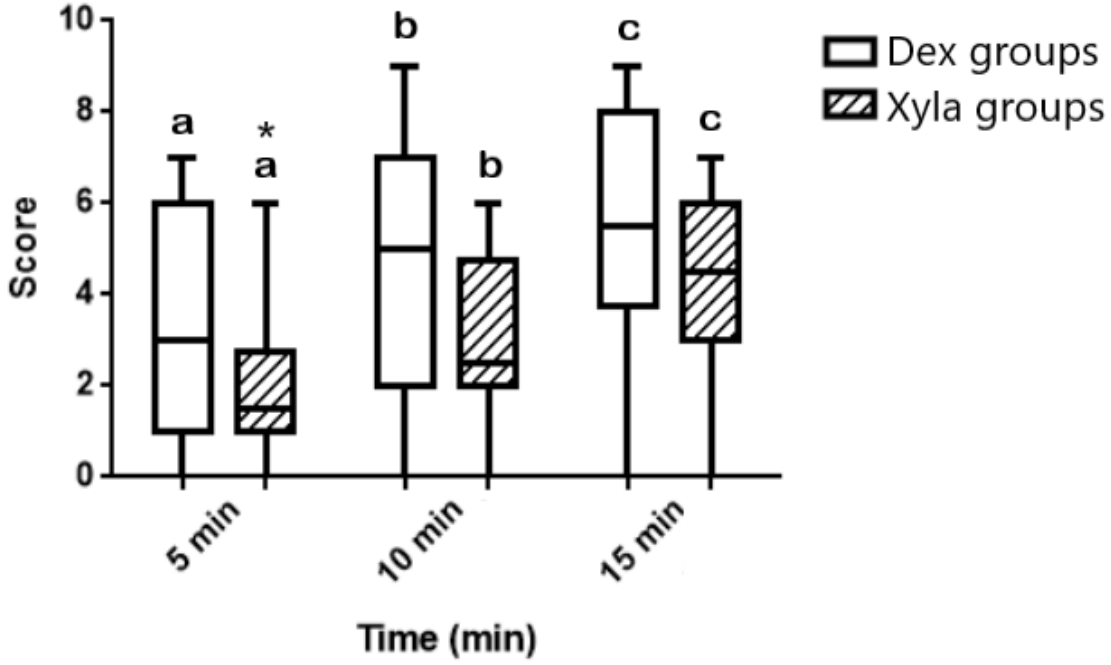
FIGURES

Figure 1. Sedation scores 5, 10 and 15 minutes after premedication for Dex (Dex and DexCRI) and Xyla (Xyla and XylaCRI) groups



Sedation scores for Dex and Xyla groups assessed 5, 10 and 15 minutes after premedication with morphine (0.5 mg/kg [0.23 mg/lb]) and dexmedetomidine (10 µg/kg [4.5 µg/lb]) for Dex groups, or morphine (0.5 mg/kg [0.23 mg/lb]) and xylazine (0.3 mg/kg [0.14 mg/lb]) for Xyla groups. Data are expressed in median, range, 1st and 3rd interquartile. *Values in Xyla groups differ significantly from the values assessed at 5 min in Dex groups. Different letters indicate significant difference between moments within the same group. Values of $p < 0.05$ were considered significant.

APPENDIX

Sedation score system used to assess sedation degrees 5, 10 and 15 minutes after premedication

Score	Posture score
0	Able to walk/run normally
1	Moderate ataxia, able to stand up and to walk
2	Lateral/sternal recumbency, stands up under stimulation
3	Lateral recumbency, not able to stand up
	Behavior
0	Normal response to contact with assessor*
1	Slower response to assessor than normal*
2	Minimal response to assessor contact*
3	No response to assessor*
	Muscle relaxation
0	Normal
1	Slightly weak, tongue cannot be pulled out, or can be pulled out only with difficulty
2	Weak, tongue can be pulled out, but the dog is able to withdraw it
3	Very weak, the tongue can easily be pulled out and the dog is unable to withdraw it

*Contact with assessor included clapping near the dog's ear and calling the dog's name.

Sedation scores consisted of the sum of all three categories assessed. Adapted from another study[8]

TABLES

Table 1. Mean ± SD for cardiorespiratory parameters monitored before (BL) and during the OH procedures

Variable	Group	Moment					
		BL	**INI**	**LO**	**RO**	**C**	**END**
MAP (mmHg)	Dex	118.7 ± 24.45^{b}	85.7 ± 7.99^{a}	105.5 ± 9.87^{b}	108.9 ± 13.96^{b}	109.8 ± 16.46^{b}	104.5 ± 14.02^{b}
	DexCRI	115.67 ± 18.49^{b}	86.11 ± 24.6^{a}	116.22 ± 20.32^{b}	119.22 ± 17.73^{b}	111.78 ± 18.75^{ab}	101.44 ± 17.88^{ab}
	Xyla	108.33 ± 16.43^{bc}	81.33 ± 9.51^{a}	124.44 ± 12.06*^{b}	124.67 ± 13.81^{b}	117.56 ± 15.01^{bc}	104 ± 12.19^{c}
	XylaCRI	123.3 ± 31.77^{c}	71.62 ± 10.18^{a}	109.82 ± 12.3^{bc}	113.82 ± 12.13^{c}	104.54 ± 17.2^{bc}	87.19 ± 13.31*^{ab}
Temp (˚C)	Dex	38.41 ± 0.63^{a}	37.71 ± 0.95^{a}	37.42 ± 0.95^{a}	37.51 ± 0.95^{a}	37.33 ± 0.94^{a}	37.28 ± 0.92^{a}
	DexCRI	38.68 ± 0.43^{a}	37.64 ± 0.63^{b}	37.38 ± 0.58^{b}	37.42 ± 0.63^{b}	37.4 ± 0.55^{b}	37.26 ± 0.53^{b}
	Xyla	38.82 ± 0.73^{a}	37.66 ± 0.72^{b}	37.54 ± 0.82^{b}	37.59 ± 0.81^{b}	37.56 ± 0.85^{b}	37.57 ± 0.87^{b}
	XylaCRI	38.82 ± 0.73^{a}	37.66 ± 0.72^{ab}	37.54 ± 0.82^{ab}	37.59 ± 0.81^{ab}	37.56 ± 0.85^{ab}	37.57 ± 0.87^{b}
$EtCO_2$ (mmHg)	Dex	-	49.67 ± 5.2^{a}	48 ± 6.86^{a}	53.5 ± 7.09^{a}	50.2 ± 7.08^{a}	46 ± 4.32^{a}
	DexCRI	-	43.87 ± 14.36	49.37 ± 13.33	51.12 ± 14.58	45.5 ± 13.97	47.89 ± 11.4
	Xyla	-	47.87 ± 4.97	52.25 ± 5.01	48.87 ± 6.73	51.12 ± 3.76	51 ± 1.69
	XylaCRI	-	51.3 ± 7.76	51.3 ± 6.58	48.3 ± 6.78	47 ± 6.05	49.6 ± 5.44

*Within a variable and moment, values differ significantly from those in group Dex. Different superscript letters indicate significant differences between moments in the same group.

Values of $p < 0.05$ were considered significant. BL = baseline values, measured before premedication; INI = start of surgical procedure, right after first incision; LO = ligature of the left ovary pedicle; RO = ligature of the right ovary pedicle; C = ligature of the cervix; END = end of surgical procedure.

Table 2. Median (range) for cardiorespiratory parameters monitored before (BL) and during the OH procedures

Variable	Group	Moment					
		BL	**INI**	**LO**	**RO**	**C**	**END**
HR (bpm)	Dex	116 (71-160)	75.5 (46-128)*	85.5 (45-120)*	77.5 (60-135)*	80 (47-142)*	79 (43-150)*
	DexCRI	112 (81-160)	74 (59-156)	71 (44-110)	84 (44-134)	72 (48-110)	67 (48-150)
	Xyla	125 (90-196)	87 (78-136)	114 (85-122)	119 (68-147)	109 (86-195)	112 (93-191)
	XylaCRI	112 (76-212)	79 (55-107)*	82 (43-108)*†	82 (53-98)*†	82 (51-94)*†	81 (46-100)*†
RR (bpm)	Dex	33.5 (16-140)	13 (9-35)*	19 (5-42)	19.5 (8-44)*	14 (0-30)*	19.5 (10-39)
	DexCRI	33 (20-120)	16 (6-54)	25 (4-83)	18 (9-80)	16 (5-88)	21 (4-87)
	Xyla	28 (12-80)	26.5 (9-83)	18 (9-66)	29 (15-74)	16 (10-53)	19 (12-28)
	XylaCRI	28 (16-120)	12 (7-34)*	22 (6-72)	17 (6-44)*	16 (4-72)	14 (8-34)*
SpO_2 (%)	Dex	-	95 (88-99)	97 (94-100)	94.5 (91-100)	97 (94-100)	96.5 (92-100)
	DexCRI	-	96 (92-100)	96 (91-100)	96 (91-100)	97 (82-100)	95 (93-100)
	Xyla	-	96.5 (92-100)	97 (94-100)	97 (94-99)	97.5 (94-100)	96.5 (94-100)
	XylaCRI	-	95 (92-100)	96 (91-100)	96 (90-100)	95 (91-100)	97 (90-100)

*Within a variable and protocol, values differ significantly from those at BL.

†Within a variable and moment, values in group XylaCRI differ significantly from those in all other groups.

Values of $p < 0.05$ were considered significant. BL = baseline values, measured before premedication; INI = start of surgical procedure, right after first incision; LO = ligature of the left ovary pedicle; RO = ligature of the right ovary pedicle; C = ligature of the cervix; END = end of surgical procedure.

Table 3. Median (range) for scores assessed during the perioperative period

Score	Dex	DexCRI	Xyla	XylaCRI
Transoperative relaxation	3 (2-3)	2 (1-3)	2 (1-3)	3 (1-3)
Melbourne pain scale	3 (0-8)	4 (0-9)	5 (2-11)	4 (1-8)

Values of $p < 0.05$ were considered significant.

SUPPLEMENTARY MATERIAL

University of Melbourne Pain Scale

Category	Descriptor	Score
Physiologic data		
a.	Physiologic data within reference range	0
b.	Dilated pupils	2
c. Choose one	Percentage increase in heart rate relative to preprocedural rate	
	>20%	1
	>50%	2
	>100%	3
d. Choose one	Percentage increase in respiratory rate relative to preprocedural rate	
	>20%	1
	>50%	2
	>100%	3
e.	Rectal temperature exceeds reference range	1
f.	Salivation	2
Response to palpation		
Choose one	No change from preprocedural behaviour	0
	Guards/reacts* when touched	2
	Guards/reacts* before touched	3
Activity		
Choose one	At rest – sleeping or semiconscious	0
	At rest – awake	1
	Eating	0

	Restless (pacing continuously, getting up and down)	2
	Rolling, thrashing	3
Mental status		
Choose one	Submissive	0
	Overtly friendly	1
	Wary	2
	Aggressive	3
Posture		
a.	Guarding or protecting affected area (including fetal position)	2
b. Choose one	Lateral recumbency	0
	Sternal recumbency	1
	Sitting or standing, head up	1
	Standing, head hanging down	2
	Moving	1
	Abnormal posture (eg, prayer position, hunched back)	2
Vocalisation**		
Choose one	Not vocalising	0
	Vocalising when touched	2
	Intermittent vocalisation	2
	Continous vocalisation	3

* Includes turning head toward affected area; biting, licking, or scratching at the wound; snapping at the handler; or tense muscles and a protective (guarding) posture. ** Does not include alert barking.

CAPITULO 3

CONSIDERAÇÕES FINAIS

Ao se comparar a DEX à xilazina como parte de protocolos balanceados contendo morfina, lidocaína e cetamina para realização de OH em cadelas hígidas, observou-se que tanto os protocolos com infusão contínua de α2-agonistas quanto os protocolos com o uso destes fármacos apenas na MPA foram adequados para a realização destes procedimentos, visto que não houve diferença nos escores de relaxamento transoperatório e escores de dor pós-operatória, e nenhum animal necessitou de resgate analgésico no período pós-operatório imediato.

No entanto, os protocolos sem infusão contínua de α2-agonistas podem ser mais adequados para OH, uma vez que proporcionam menores alterações cardiorrespiratórias como um todo. Deve-se atentar ao uso excessivo de fármacos na rotina, a fim de reduzir os efeitos adversos, evitar recuperações prolongadas e sedações excessivas.

O grupo com os menores tempos de extubação foi o grupo Xila. Contudo, o tempo de extubação foi maior no grupo XilaCRI quando comparado aos demais grupos, o que sugere que a xilazina em infusão contínua prolongou o tempo de recuperação nestes animais, mas a DEX não.

As arritmias observadas (bloqueio atrioventricular de segundo grau e arritmia sinusal) foram brandas e em poucos animais, sem importância clínica para realização destes procedimentos. Isto sugere que tanto a xilazina quanto a DEX podem ser utilizadas de forma segura como parte de protocolos de anestesia total intravenosa, desde que estes pacientes estejam monitorados de forma adequada, devidamente intubados e com suplementação de oxigênio. Assim como qualquer procedimento anestésico-cirúrgico, existem riscos, considerando que alguns animais necessitaram de ventilação assistida devido a ocorrência de apneia e/ou hipercapnia.

Não houve diferença para os custos calculados entre os protocolos contendo xilazina e DEX. No entanto, pensando em grandes volumes de

animais, esta diferença pode se tornar significativa, e os protocolos contendo xilazina podem ser preferidos neste cenário.

Mais estudos são necessários a fim de elucidar as vantagens e desvantagens de diferentes α2-agonistas como parte de protocolos balanceados em cães. A literatura é escassa com relação ao uso da xilazina em infusão contínua em cães e, conforme os resultados obtidos neste estudo, esta técnica se mostrou eficaz e segura dentro de um protocolo de anestesia total intravenosa para realização de OH. Contudo, mais estudos são imprescindíveis para avaliar o uso da xilazina em infusão contínua em outros procedimentos cirúrgicos.

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Pró-Reitoria de Pesquisa e Pós-Graduação
Comissão de Ética em Pesquisa no Uso de Animais

Curitiba, 16 de novembro de 2017.

PARECER DE PROTOCOLO DE PESQUISA

REGISTRO DO PROJETO: 01187 – 1ªversão

TÍTULO DO PROJETO: *PROTOCOLOS ANESTÉSICOS VIÁVEIS E RENTÁVEIS PARA CADELAS SUBMETIDAS A OSH EM CAMPANHAS DE CASTRAÇÃO*

PESQUISADOR RESPONSÁVEL

CLAUDIA TURRA PIMPÃO

EQUIPE DE PESQUISA

Manoella Ourique Muller, Luiz Guilherme Achcar Capriglione, Eros Luiz de Sousa, Josiane Batista Mendes, Luciana Galeb, Gustavo Alessio Trevisan, Paola Lucas da Silva, Thays Barbosa Vargas, Guilherme Campos

INSTITUIÇÃO

Pontifícia Universidade Católica do Paraná

ESCOLA / CURSO

Escola de Ciências da Vida

VIGÊNCIA DO PROJETO	Abril/2017 a Julho/2018	**QUANTIDADE DE ANIMAIS**	48
ESPECIE/LINHAGEM	*Canis lupus familiaris*	**Nº SISBIO** (Somente animais de vida livre)	Não se aplica
SEXO	M/F	**ATIVIDADES** (Somente animais de vida livre)	Não se aplica
IDADE / PESO	6 e 7 anos / Variados	**ESPECIÉ – GRUPO TAXONÔMICOS** (de vida livre)	Não se aplica
ORIGEM DO ANIMAL	CEV – PUCPR / Particulares	**LOCAL (IS)** (Somente animais de vida livre)	Não se aplica

O colegiado da CEUA certifica que este protocolo que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto homem), para fins de pesquisa cientifica, encontra-se de acordo com os preceitos da Lei nº 11.794/2018 e Decreto nº 6.899/2009, e com as normas editadas pelo CONCEA e foi **APROVADO** pela CEUA - PUCPR em reunião de colegiado. Se houver mudança do protocolo o pesquisador deve enviar um relatório á CEUA descrevendo de forma clara e sucinta, a parte do protocolo a ser modificado e as suas justificativas. Se a pesquisa, ou parte dela for realizada em outras instituições, cabe ao pesquisador não iniciar antes de receber a autorização formal para a sua realização. O documento que autoriza o início da pesquisa deve ser carimbado e assinado pelo responsável da instituição e deve ser mantido em poder do pesquisador responsável, podendo ser requerido por esta CEUA em qualquer tempo.

Atenciosamente,

Prof. Carlos Eduardo Camargo
Coordenador Adjunto
Comissão de Ética no Uso de Animais