UADY
POSGRADO INSTITUCIONAL EN CIENCIAS AGROPECUARIAS Y MANEJO DE RECURSOS NATURALES TROPICALES

EFECTO ANESTÉSICO DE LA INFUSIÓN CONSTANTE INTRAOPERATORIA DE FENTANILO-LIDOCAÍNA-KETAMINA EN CABRAS ANESTESIADAS CON ISOFLURANO O PROPOFOL Y SOMETIDAS A ABOMASOTOMÍA

TESIS

PRESENTADA COMO REQUISITO
PARA OBTENER EL GRADO DE:

MAESTRA EN CIENCIAS AGROPECUARIAS

POR:

Médico Veterinario Zootecnista
PERLA IVETTE VELÁZQUEZ DELGADO

Directores:
Dr. Juan Felipe de Jesús Torres Acosta
Dr. Eduardo Gutiérrez Blanco
Dr. Tarisai Brighton Dzikiti

POSGRADO INSTITUCIONAL
CIENCIAS AGROPECUARIAS Y MANEJO
DE RECURSOS NATURALES TROPICALES

Mérida, Yuc., México, junio de 2018.

ALUMNA : MÉDICO VETERINARIO ZOOTECNISTA
PERLA IVETTE VELÁZQUEZ DELGADO

SÍNODO DEL EXAMEN DE TESIS DE GRADO

DR. ARMANDO AGUILAR CABALLERO
CCBA-UADY

DR. ANTONIO ORTEGA PACHECO
CCBA-UADY

DR. CARLOS ACEVEDO ARCIQUE
CCBA-UADY

M. EN C. RAMÓN CÁMARA SARMIENTO

CCBA-UADY

M. EN C. LEONARDO GUILLERMO CORDERO

CCBA-UADY

MÉRIDA, YUCATÁN, JULIO DEL 2018

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AGRADECIMIENTOS

.

Al Consejo Nacional de Ciencia y Tecnología de México (CONACYT) por todo el apoyo que me brindó a lo largo del programa de Maestría. Sin la beca de esta institución no hubiera sido posible llevar a cabo esta meta profesional y al Proyecto CONACYT Ciencia Básica No. CB-2013-01221608, por el financiamiento de este proyecto.

Al **Dr. Eduardo Gutiérrez Blanco**, por toda la paciencia y su valioso tiempo. Gracias por todo el apoyo, gracias por creer en mí, usted ha sido un gran ejemplo y deseo contar siempre con su sabiduría y amistad.

Al **Dr. Felipe Torres Acosta**, por la acertada orientación, el soporte y discusión crítica que me permitió un buen aprovechamiento en el trabajo realizado y a su equipo de trabajo por sus aportes, críticas, comentarios y sugerencias durante el desarrollo de esta investigación.

Al Dr. **Tarisai Brighton Dzikiti, s**us aportaciones a esta tesis han sido de mucha importancia, al trasmitirme su experiencia en el estudio del manejo anestésico de esta especie.

A mi comité tutorial por su desinteresada colaboración y asistencia profesional y por su sostenido apoyo moral.

A mis padres y hermanas por ser el pilar fundamental en todo lo que soy, en toda mi educación, tanto académica, como de la vida, por su incondicional apoyo perfectamente mantenido a través del tiempo.

Al equipo de trabajo, **Nimsy Velázquez, Eduardo Martínez Briceño, Luis Casanova y el equipo de trabajo de la Unidad de Enseñanza Medica** gracias por su ayuda, paciencia y todo el apoyo brindado durante la realización de este estudio.

A mis compañeros de generación y amigos por el apoyo mutuo en nuestra formación profesional: **Omar Castillo Trujillo, Gladys Noh Cuxim, José Ortíz Esquivel, Eduardo Ramos, Eduardo Avalos Borges y Rafael Torres Fajardo.**

Ramiro Vera Gamas por su apoyo, compresión y paciencia, por acompañarme en esta etapa tan importante y brindarme su amor.

UN AGRADECIMIENTO ESPECIAL PARA TODAS AQUELLAS PERSONAS QUE DE UNA U OTRA FORMA CONTIBUYERON A ESTE TRABAJO**.**

RESUMEN

Las técnicas de anestesia balanceada son comunes para el mantenimiento de la anestesia general. La combinación de fármacos adyuvantes optimiza la acción del anestésico inhalado o inyectable, a través de sus diferentes mecanismos de acción, reduciendo los requerimientos anestésicos de estos, mejorando la calidad de la analgesia y la estabilidad cardiopulmonar. La anestesia parcial intravenosa con isoflurano y la anestesia total intravenosa con propofol, son técnicas utilizadas para la anestesia general en cabras, ya sea con fines quirúrgicos clínicos y/o de investigación. El fentanilo, la lidocaína y ketamina, se han utilizado exitosamente para este propósito. El objetivo del presente trabajo fue comparar el efecto anestésico, analgésico, cardiopulmonar y conductual de la infusión constante de fentanilo-lidocaína-ketamina en cabras anestesiadas con propofol o isoflurano sometidas a abomasotomía. Se realizó un estudio clínico prospectivo no cegado con 18 cabras programadas para abomasotomía, se premedicaron con fentanilo (10 μg kg^{-1}), lidocaína (2 mg kg^{-1}) y ketamina (1.5 mg kg^{-1}) por vía intravenosa. Se indujo a la anestesia con propofol y se asignaron aleatoriamente a los siguientes grupos: TIVA, infusión continua (CRI) de propofol a 0.3 mg kg^{-1} min^{-1} o PIVA, isoflurano vaporizado en oxígeno, con una fracción espirada inicial (FE´Iso) de 1.2%, ambos grupos recibieron una CRI de fentanilo (10 μg kg^{-1} $hora^{-1}$), lidocaína (50 μg kg^{-1} min^{-1}) y ketamina (50 μg kg^{-1} min^{-1}). La administración de los anestésicos se ajustó de manera intermitente de acuerdo con los signos evaluados para la profundidad anestésica. Se monitorizaron las variables cardiopulmonares, gases sanguíneos, FE´Iso y la tasa de CRI de propofol durante la cirugía. La recuperación anestésica fue cronometrada y la calidad fue evaluada. Los datos se analizaron utilizando ANOVA de mediciones repetidas y T de Student ($p < 0,05$). La dosis media de propofol para el mantenimiento anestésico fue de 0,44±0.06 mg kg^{-1} min^{-1} en TIVA y la media general de FE′Iso fue de 0,81±0,2% en PIVA. La función cardiopulmonar fue adecuada en ambos grupos. Los tiempos de recuperación en minutos desde el final de la anestesia fueron similares en ambos grupos. La calidad de la recuperación fue satisfactoria en el grupo PIVA, mientras que en el grupo TIVA fue regular, observándose signos conductuales anormales después del tratamiento. En conclusión, a las dosis administradas, la CRI de fentanilo-lidocaína-ketamina en cabras anestesiadas con propofol o isoflurano produjo una anestesia satisfactoria durante la cirugía con cambios mínimos en la función cardiopulmonar. Sin embargo, las recuperaciones después de la combinación de propofol-fentanilo-lidocaína-ketamina son de mala calidad. **Palabras clave**: Anestesia total intravenosa, anestesia parcial intravenosa, cabras, propofol, isoflurano.

SUMMARY

Balanced anesthetic techniques are nowadays popular for maintenance of general anesthesia. When combining adjuvants drugs with different mechanisms of action, the action of the anesthetic is optimized, analgesia is enhanced and a reduction of the requirements of injectable or inhaled anesthetics is achieved, leading to an improvement on cardiopulmonary stability. Partial intravenous anesthesia with isoflurane (PIVA) and total intravenous anesthesia with propofol (TIVA) are both anesthetic techniques used for anesthesia in goats for surgery and research. Fentanyl, lidocaine and ketamine have been successfully used for this purpose. The aim of this study was to compare the anesthetic, analgesic, cardiovascular and behavioral effects of a constant rate infusion of fentanyl- lidocaine-ketamine in propofol or isoflurane anesthetized goats undergoing abomasotomy. Eighteen goats scheduled for abomasotomy were included in a randomized, prospective, non-blinded, clinical study. All the goats were premedicated with fentanyl (10 μg kg^{-1}), lidocaine (2 mg kg^{-1}) and ketamine (1.5 mg kg^{-1}) administered intravenously. Anesthesia was induced with propofol and the goats were randomly assigned to: TIVA group, constant rate infusion (CRI) of propofol at 0.3 mg kg^{-1} $minute^{-1}$ or PIVA group, isoflurane vaporized in oxygen with initial end-tidal (FE′Iso) concentration of 1.2%, in addition, to CRI of fentanyl (10 μg kg^{-1} hour-1), lidocaine (50 μg kg^{-1} $minute^{-1}$) and ketamine (50 μg kg^{-1} $minute^{-1}$) Anesthetic administration was adjusted intermittently according to assessed signs of anesthetic depth. Cardiopulmonary parameters, arterial blood gases-gas, FE′Iso and the CRI rates were recorded intermittently. Anesthetic recovery was timed, and quality scored. Data were analyzed using ANOVA and Student's T test ($p < 0.05$). The mean propofol dose for anaesthetic maintenance was the 0.44±0.06 mg kg^{-1} $minute^{-1}$ in TIVA. Meanwhile the mean FE′Iso requirements were 0.81±0.2% in PIVA. Cardiopulmonary function was well maintained in both groups. Recovery times in minutes from the end of anaesthesia were similar in both groups. Quality of recovery was recorded as satisfactory in group PIVA, whereas in group TIVA it was recorded as regular and abnormal behavioural signs were observed after the treatment. It is concluded that at the doses administered, the CRI of fentanyl-lidocaine-ketamine, on either propofol or isoflurane anaesthetized goats showed satisfactory anaesthesia during surgery, with minimal changes on cardiopulmonary function. The recoveries after the combination of propofol-fentanyl-lidocaine-ketamine are of poor quality. ***Keywords:*** anaesthesia total intravenous, anaesthesia partial intravenous, goats, propofol, isoflurane.

ÍNDICE

1. INTRODUCCIÓN.

Los caprinos, se utilizan cada vez con mayor frecuencia como modelos quirúrgicos en la experimentación animal (Larenza et al., 2005), por lo cual, es necesario someterlos a anestesia general donde, en la mayoría de los casos, se realizan bajo anestesia inhalatoria, utilizando anestésicos inyectables para la inducción anestésica, o bien en el mantenimiento anestésico (Reid et al., 1993), requiriendo dosis altas de estos para alcanzar un adecuado plano anestésico, aumentando con esto la probabilidad de efectos adversos (Steffey y Mama, 2007). En la práctica anestésica actual, no existe un agente anestésico ideal, si bien algunos tienen ventajas en ciertas áreas, otros carecen de propiedades importantes, esta problemática puede ser abordada mediante la combinación de diferentes fármacos (Tonner, 2005). El término de anestesia balanceada se basa en el uso equilibrado de diversos fármacos y técnicas anestésicas, para lograr los objetivos de la anestesia ideal a saber: analgesia, amnesia, relajación muscular, reducción o eliminación de los reflejos autonómicos y estabilidad de los sistemas corporales (Lundy, 1926; Bailey y Stanley, 1994; Valverde, 2013; Beths, 2017). Estudios recientes en cabras, han propuesto el uso de diversos fármacos con el fin de lograr este objetivo (Larenza et al., 2005; Doherty et al., 2007; Dzikiti et al., 2010; Dzikiti et al., 2011a; Dzikiti et al., 2011b; Dzikiti et al., 2014; Vieitez et al., 2017). En Medicina Veterinaria, algunos de los protocolos de anestesia balaceada, incluyen la combinación de anestésicos inhalatorios con agentes intravenosos (analgésicos y/o sedantes), técnica conocida como anestesia parcial intravenosa (PIVA) (Fujita et al., 1993; Aida et al., 1996; Galloway et al., 2004; White, 2015) o bien, el mantenimiento de la anestesia general basado exclusivamente por vía intravenosa (TIVA) (White, 2015; Beths, 2017).

La combinación de anestésicos inhalatorios con agentes intravenosos, produce una mejora en los parámetros cardiopulmonares debido a la reducción en los requerimientos del agente inhalatorio y a la hipotensión asociada a este (Fujita et al., 1993; Aida et al., 1996; Galloway et al., 2004; Funes et al., 2015), algunos fármacos empleados en caprinos para esta técnica son la ketamina (Doherty et al., 2007; Beier et al., 2014; Kumar et al., 2014), la lidocaína (Doherty et al., 2007) y el fentanilo (Dzikiti et al., 2011b).

No obstante, TIVA es una alternativa al uso de anestésicos inhalatorios, gracias al uso de fármacos con escaso poder acumulativo y rápida recuperación (Dzikiti, 2013; Beths, 2017),

siendo el propofol el agente más adecuado para esta técnica dada sus propiedades farmacocinéticas que le permiten una rápida y corta acción (Bettschart-Wolfensberger et al., 2000). Sin embargo, sus pobres propiedades analgésicas lo hacen insatisfactorio como agente único (Smith et al., 1994; Bettschart-Wolfensberger et al., 2000), por lo que debe considerarse su combinación con otros fármacos durante procedimientos dolorosos (Sneyd, 2004; Beths, 2008). Diversos estudios en cabras han demostrado resultados satisfactorios para la obtención de anestesia quirúrgica, generando mínimos efectos adversos (Branson, 2007) al asociar el propofol a fármacos con potencial analgésico, tales como el fentanilo (Dzikiti et al., 2011b; Vieitez et al., 2017), la ketamina (Larenza et al., 2005) y la lidocaína (Vieitez et al., 2017).

Por lo cual, el objetivo del presente trabajo fue comparar el efecto anestésico, analgésico, cardiopulmonar y conductual de la infusión constante de fentanilo-lidocaína-ketamina en cabras anestesiadas con propofol o isoflurano sometidas a abomasotomía.

2. REVISIÓN DE LITERATURA

2.1. Generalidades de la anestesia.

El término anestesia, derivado del término del griego ἀναισθησία, significa "insensibilidad", es utilizado para describir un estado transitorio y reversible de depresión de la actividad del tejido nervioso local, regional o dentro del sistema nervioso central (SNC), inducido por fármacos y caracterizado por la pérdida de consciencia, percepción, motilidad y reflejos, manteniendo un equilibrio en las constantes vitales (Aitkenhead y Smith, 1990; Short, 2003, Thurmon y Short, 2007).

2.1.1. Tipos de anestesia.

La anestesia se clasifica de acuerdo con el tipo de fármaco, método y vía de administración. De acuerdo con la vía de administración empleada, los procedimientos de anestesia general se clasifican en dos grupos: anestesia inhalatoria (los gases o vapores anestésicos se inhalan en combinación con oxígeno) y la anestesia inyectable (las soluciones anestésicas se administran por vía intravenosa, intramuscular y subcutánea). Actualmente, ambas técnicas están ampliamente extendidas y cada una presenta tanto ventajas como inconvenientes (Thurmon y Short, 2007; Beths, 2017).

En la práctica anestésica actual, no existe un agente anestésico ideal. Aunque algunos fármacos tienen ventajas en ciertas áreas, carecen de otras propiedades importantes, por lo que un anestésico ideal, puede ser abordado mediante la combinación de diferentes fármacos (Woodbridge, 1957; Tonner, 2005).

El concepto de combinar varios fármacos con diferente mecanismo de acción fue concebido por primera vez por George W. Crile en 1910, con la teoría llamada “anociasociación”, este sugirió el uso de una anestesia general ligera junto con anestesia local, para impedir la transmisión del estímulo nocioceptivo (Crile, 1910). En 1926, John S. Lundy propuso el término de anestesia balanceada, la cual se basaba en el uso

equilibrado de agentes y técnicas (por ejemplo, premedicación, anestesia regional, anestesia general) para lograr los diferentes objetivos deseados durante la anestesia (analgesia, amnesia, relajación muscular y reducción o eliminación de los reflejos autonómicos, mientras se mantiene la homeostasis) (Lundy, 1926; Bailey y Stanley, 1994; Valverde, 2013; Beths, 2017).

2.2. Anestesia general inyectable

Las técnicas de anestesia general inyectable, fija o parenteral, agrupa aquellas que se administran por rutas diferentes a la respiratoria; la vía de administración más común es la intravenosa seguida de la intramuscular (Thurmon y Short, 2007; Beths, 2017).).

Existen tres técnicas básicas de administración de anestésicos inyectables por vía intravenosa:

1) Administración en una dosis única de anestésico (eficaz para efectuar la inducción de la anestesia y para procedimientos de corta duración).
2) Redosificación mediante bolos adicionales administrados a dosis efecto.
3) La infusión continua a una tasa fija o variable (Beths, 2008; Waelbers et al., 2009; Pypendop, 2014; Beths, 2017).

La administración de un fármaco mediante bolos intermitentes produce oscilaciones en la concentración plasmática del fármaco, lo que puede llevar a variaciones en la profundidad anestésica y la presencia de efectos secundarios indeseables. A diferencia del empleo de la infusión continua intravenosa, que permite el mantenimiento constante de las concentraciones plasmáticas del fármaco (Pypendop, 2014; Beths, 2017).

La anestesia balanceada, empleando fármacos inyectables, se obtiene a partir del conocimiento de la farmacodinamia y farmacocinética de estos, asociando de esta manera diversos fármacos con distintos mecanismos de acción, que sumados producen relajación muscular, analgesia, inconsciencia y protección neurovegetativa. Esta asociación también

tiene como objetivo promover una mínima depresión cardiopulmonar y un mínimo efecto acumulativo (Lundy, 1926; Bailey y Stanley, 1994; Muir, 1994; Thurmon et al., 1996).

2.2.1. Propofol.

Es un isopropil-fenol (2,6-diisopropilfenol) derivado alquil-fenólico, utilizado para la inducción y mantenimiento de la anestesia, altamente lipofílico, formulado como una emulsión acuosa, se caracteriza por su mínimo efecto acumulativo, su rápida acción y recuperación (Posner y Burns, 2009; Clarke et al., 2014; Berry, 2015).

2.2.1.1. Mecanismo de acción.

Actúa inhibiendo los receptores del ácido γ-aminobutírico (GABA), aumentado la concentración de este neurotransmisor en el SNC, además produce una reducción generalizada en la actividad metabólica cerebral y en la perfusión intracraneal y cerebral (Branson y Gross, 1994; Posner y Burns, 2009; Berry, 2015).

2.2.1.2. Farmacocinética y farmacodinamia.

El propofol, se distribuye rápidamente y se convierte en metabolitos inactivos, su aclaramiento rápido se produce en la medida en que este se libera de los tejidos, por lo que no se observa una sedación residual. Es altamente lipofílico y biotransformado en el hígado en conjugados glucurónidos inactivos, implicando al sistema citocromo P450. Los metabolitos son excretados en la orina. Sin embargo, el aclaramiento puede ser mayor que la fluctuación sanguínea hepática, y se cree que los mecanismos extrahepáticos (por ejemplo, pulmón y riñón) contribuyen a este (Posner y Burns, 2009; Clarke et al., 2014; Berry, 2015).

2.2.1.3. Efectos secundarios.

En el sistema cardiovascular, induce hipotensión por la depresión de la contractibilidad miocárdica, vasodilatación arterial y venodilatación (Ilkiw et al., 1992; Branson y Gross, 1994).

En pequeños rumiantes, se ha observado, que produce una depresión respiratoria y cardiovascular a dosis-dependiente (Upton et al., 2009). La depresión respiratoria, se manifiesta por un descenso en el pH, como resultado de un incremento de la $PaCO_2$ y por un descenso en la frecuencia respiratoria (FR) (Andaluz et al., 2005). El descenso de la FR tras la inducción anestésica puede llegar a producir apnea en cabras (Pablo et al., 1997; Dzikiti et al., 2009).

Además de la depresión cardiopulmonar, se ha asociado a otros efectos no deseados tras su administración en pequeños rumiantes como son una salivación excesiva, opistótonos (Torres et al., 2012) o mioclonos (Pablo et al., 1997; Dzikiti et al., 2009).

2.2.2. Lidocaína.

La lidocaína, es un anestésico local, perteneciente al grupo de las amidas, de potencia intermedia y de acción corta, bloqueador no selectivo de los canales de sodio. Reduce los requerimientos de los anestésicos principalmente por sus características analgésicas y sedativas. Tiene un rápido tiempo de latencia (2-5 minutos) y la duración de su efecto es variable dependiendo de la vía de administración (Thomas et al., 2004; Webb y Pablo, 2009).

Es utilizado principalmente, tanto en medicina veterinaria como humana, para producir analgesia en regiones anatómicas circunscritas (Borer, 2006), sin embargo, al ser administrado sistémicamente, ha demostrado ser eficaz en el tratamiento del dolor agudo y el dolor postoperatorio (Gaynor y Muir, 2009).

Existe un creciente interés sobre el uso de la lidocaína mediante infusión continua durante la anestesia, ya que, con su uso, se reducen los requerimientos de los anestésicos inhalatorios minimizándose los efectos adversos de estos (Doherty y Frazier, 1998; Pypendop y Ilkiw, 2005).

2.2.2.1. Mecanismo de acción.

Bloquea los canales de sodio dependientes de voltaje presentes en la membrana del axón. Para llevar a cabo dicha acción, tienen afinidad por receptores específicos situados en el interior del canal, esto impide el paso del ion sodio a través de sus canales, inhibiendo la generación y conducción del impulso nervioso (Botana, 2002; McCleane, 2007; Webb y Pablo, 2009).

2.2.2.2. Farmacocinética y farmacodinamia.

La absorción de la lidocaína desde los tejidos va a depender principalmente del grado de irrigación del lugar y de la asociación o no a un vasoconstrictor. Posterior a su absorción, se biotransforma en el hígado por acción de oxidasas de función mixta, dando origen a dos metabolitos, monoetilglicina xilidina y glicina xilidina, que también tienen acción anestésica, su eliminación es renal (en humanos) en menos del 2% (Catterall y Mackie, 2001; Gaynor y Muir, 2009; Webb y Pablo, 2009).

2.2.2.3. Efectos secundarios.

En algunos estudios con animales la lidocaína ha demostrado un efecto inotropo negativo mediado por un efecto con los canales de sodio y calcio (McCleane, 2007).

2.2.3. Ketamina.

La ketamina 2-(-0-clorofenol)-2-(metilamino)-ciclohexanona clorhidrato, es un derivado de la fenciclidina, antagonista de los receptores NMDA (N-metil-D-aspartato), utilizado como anestésico general; que, a dosis bajas, puede contribuir de manera substancial a la analgesia, minimizando la sensibilización del SNC (Prassinos et al., 2005; Cruz et al., 2009; Posner y Burns, 2009; Hellyer et al., 2011).

2.2.3.1. Mecanismo de acción.

La ketamina se une de manera no competitiva al receptor NMDA. De esta forma previene la unión del neurotransmisor excitatorio glutamato, resultando en una depresión de la actividad

de los sistemas talamo-cortical, límbico y reticular activado (Prassinos et al., 2005). La analgesia atribuida a la ketamina podría estar mediada al menos por dos mecanismos: La activación de los receptores opioides (μ-κ) y a la prevención de sensibilización central y periférica, además de la sumación temporal (Cruz et al., 2009). A su vez, interviene en la actividad inflamatoria, interactuando con el reclutamiento de células inflamatorias, la producción de citoquinas y la regulación de los mediadores inflamatorios, produciendo un efecto antiinflamatorio limitando la respuesta inflamatoria sistémica (Loix et al., 2011).

2.2.3.2. Farmacocinética y farmacodinamia.

La ketamina se distribuye rápidamente a todos los tejidos corporales en especial en el tejido adiposo, hígado, pulmón y cerebro. Su biotransformación ocurre en el hígado por procesos de metilación y el metabolito resultante es la norketamina, el cual pasa por procesos de hidroxilación, haciéndolo más soluble en agua y facilitando su eliminación en orina (Cruz et al., 2009; Gaynor y Muir, 2009; Posner y Burns, 2009).

2.2.3.3. Efectos secundarios.

En infusiones constantes prolongadas, aún a dosis subanestésicas, pueden presentarse algunos casos de disforia (Wagner et al., 2002).

2.2.4. Fentanilo.

El fentanilo es un opioide semisintético, agonista μ puro, altamente liposoluble y 100 veces más potente que la morfina. Se caracteriza por su rápida acción y corta duración, así como su gran potencialidad analgésica (Sumano y Ocampo, 2006; Gaynor y Muir,2009; Hellyer et al., 2001; KuKanich y Wiese, 2015). Se ha observado que la administración en IC de fentanilo produce una reducción de la CAM de los gases anestésicos en cabras (Dzikiti et al., 2011b).

2.2.4.1. Mecanismo de acción.

El fentanilo se une de manera reversible al receptor opioide μ, activando varios tipos de proteína G e inhibiendo la actividad de la enzima adenil-ciclasa, esto activa las corrientes de los receptores operados por el ion potasio y suprime las corrientes de voltaje del ion calcio. Esta disminución de la liberación de calcio previene la liberación de neurotransmisores, como la sustancia P en el SNC (Gaynor y Muir, 2009; Kukanich y Papich, 2009).

2.2.4.2. Farmacocinética y farmacodinamia.

Debido a su alta liposolubilidad, el fentanilo se distribuye rápidamente del plasma al SNC, y posteriormente se redistribuye del SNC a tejidos, como el tejido graso y el músculo esquelético, por lo que la concentración plasmática disminuye, siendo responsable de la rápida terminación del efecto clínico. Sin embargo, a grandes dosis o infusiones prolongadas es necesaria la biotransformación hepática y excreción renal para que desaparezca el efecto clínico. La vida media de eliminación tras la administración de un bolo de fentanilo es de 2 a 3 horas en cabras (Carroll et al., 1999).

2.2.4.3. Efectos secundarios.

Se ha descrito una importante depresión a nivel respiratorio, tras la administración de un bolo o una IC de fentanilo, reflejada por un incremento en la PaCO2 y un descenso en la FR (Thomasy et al., 2006; Dzikiti et al., 2010). De igual forma se ha documentado la depresión del sistema cardiovascular, posterior a su administración en cabras, observándose un marcado descenso de la presión arterial media (PAM) y de la frecuencia cardiaca (FC) (Liehmann et al., 2006; Dzikiti et al., 2011b). Por otro lado, el tiempo de administración de una IC de fentanilo durante el mantenimiento anestésico presenta un efecto directo en la recuperación anestésica, ya que, su eliminación puede verse prolongada, debido a la acumulación asociada a su alta liposolubilidad (Sano et al., 2006). De igual manera, se han demostrado cambios conductuales asociados a su administración en rumiantes, debido a la estimulación del sistema nervioso central (SNC) (Valverde y Doherty, 2008; Lin, 2014), produciendo un aumento en la vocalización y agitación (Carroll et al., 1999), movimientos

masticatorios y nistagmo (Upton et al., 2009), así como un meneo excesivo de la cola (Dzikiti et al., 2009).

2.3. Anestesia inhalatoria.

Los anestésicos inhalatorios se utilizan ampliamente para el manejo anestésico de los animales, siendo los únicos, entre los fármacos anestésicos, que se administran y en gran parte se eliminan, a través de los pulmones. Su popularidad se basa principalmente en sus características farmacocinéticas, las cuales favorecen el ajuste predecible y rápido de la profundidad de la anestesia (Steffey y Howland, 1977; Steffey y Mama, 2007; Steffey, 2009), así como su poca acumulación en el organismo, por lo que son los de elección en cirugías de larga duración. Sin embargo, producen depresión cardiopulmonar a dosis-dependiente y no poseen efecto analgésico. Debido a esto, para alcanzar un plano quirúrgico, deben administrarse dosis elevadas que acentúan sus efectos adversos (Eger, 1988).

2.3.1. Isoflurano.

El isoflurano, es actualmente el anestésico inhalatorio (AI) más utilizado, (Thurmon y Short, 2007; Steffey, 2009), debido a su corto tiempo de inducción y recuperación, gracias a su bajo coeficiente de solubilidad sangre/gas (Antognini y Eisele, 1993). Puede ser utilizado de forma segura y eficaz para la anestesia general en los animales de granja (Lin y Walz, 2014). Se han reportado valores de CAM de isoflurano en cabras que oscilan entre 1.23 (Antognini y Eisele, 1993), 1.29 (Hikasa et al., 1998), y 1.50% (Doherty et al., 2002).

2.3.1.1. Mecanismo de acción.

El mecanismo de acción preciso por el cual los anestésicos inhalatorios ejercen sus efectos no se conoce con precisión, ellos podrían interferir el funcionamiento de las células nerviosas en el cerebro por medio de su acción a nivel de la matriz lipídica de la membrana (Ludders, 1992; Thurmon y Short, 2007; Steffey, 2009).

2.3.1.2. Farmacocinética y farmacodinamia.

El isoflurano se biotransforma en un 0.2%, por procesos de desfluoronización, siendo los principales metabolitos el ácido tri-fluoroacético y flúor inorgánico, (Clarke et al., 2014; Mattos-Junior et al., 2014).

2.3.1.3. Efectos secundarios.

En el sistema cardiovascular, producen depresión dosis-dependiente de la FC, de la presión arterial (PA) y de la resistencia vascular sistémica (RVS) y, a dosis muy altas, depresión del miocardio y del gasto cardiaco (GC) (Steffey y Howland, 1977; Steffey et al., 2006; Steffey y Mama, 2007). Esta depresión cardiovascular durante el mantenimiento con anestésicos inhalatorios también se ha observado en pequeños rumiantes (Fujita et al., 1993; Hikasa et al., 1998). La disminución dosis-dependiente de la presión arterial media, sistólica y diastólica (PAM, PAS y PAD) se ha atribuido a la acción de los gases anestésicos sobre la musculatura lisa vascular, la contractilidad miocárdica y el sistema nervioso autónomo (Steffey y Howland, 1977; Mutoh et al., 1997).

A su vez, provocan una depresión respiratoria dosis-dependiente reflejada por un incremento de la PaCO2 y un descenso de la FR (Hikasa et al., 1998). Además, se ha observado que la depresión respiratoria producida por la anestesia inhalatoria en rumiantes es mayor a la registrada en monogástricos, lo cual se ha atribuido a una dificultad en la ventilación debida a un incremento en la producción de los gases ruminales y a la distensión del rumen (Ungerer et al., 1976).

2.4. Anestesia parcial intravenosa (PIVA).

La anestesia parcial intravenosa (PIVA) describe el uso de un agente inhalatorio con anestésicos intravenosos y/o analgésicos. Los fármacos más utilizados para reducir los requerimientos del agente inhalatorio son los AINES, opioides, anestésicos locales y anestésicos intravenosos, todos ellos a menores dosis de las habituales (Valverde, 2013). Los fármacos más utilizados para PIVA en cabras son ketamina (Doherty et al., 2007), lidocaína

(Doherty et al., 2007) y opioides como el fentanilo (Dzikiti et al., 2011a; Dzikiti et al., 2011b; Dzikiti, 2013).

Diversos estudios han determinado el efecto sobre los requerimientos de los anestésicos inhalatorios de la IC de diversos fármacos. Estudios en humanos y animales, han demostrado la interacción entre opiáceos y anestésicos inhalatorios, donde pequeñas dosis de opiáceos (es decir, dentro del rango analgésico) resultan en una marcada reducción de la CAM en ovejas (Funes et al., 2015), perros (Steagall et al., 2006; Ueyama et al., 2009; Gutierrez-Blanco et al., 2013), cerdos (Moon et al., 1997) y gatos (Pypendop y Ilkiw, 2005). En cabras Dzikiti et al., 2011b, determinaron que el fentanilo administrado por vía intravenosa reduce la CAM de isoflurano en un 27.6, 40.7 y 56.6% a dosis dependiente (5 μg kg^{-1}, 15 μg kg^{-1} y 30 μg kg^{-1}, respectivamente).

Por su parte, se ha determinado el efecto de la lidocaína en la disminución del CAM de anestésicos inhalatorios en humanos (Himes et al., 1997), perros 29 % (Muir et al., 2003), 18.7% (Valverde et al., 2004), 22.5% (Gutierrez-Blanco et al., 2013) y del 25% en caballos (Dzikiti et al., 2003). En cabras Doherty et al. (2007), registraron una reducción en los requerimientos de isoflurano del 18.3%, después de una dosis de carga de lidocaína (2.5 mg kg^{-1}) seguida de una IC de 100 μg kg^{-1} $minuto^{-1}$, así mismo reportaron una reducción en los requerimientos de isoflurano del 49.6% después de una dosis de carga de ketamina 1.5 mg kg^{-1} seguida de una IC (50 μg kg^{-1} $minuto^{-1}$), así como una reducción de 69.4% al combinar ambos fármacos bajo las mismas dosificaciones mencionadas con anterioridad.

2.5. Anestesia total intravenosa.

La anestesia total intravenosa (TIVA), es una técnica de anestesia general, la cual consiste en la administración de fármacos anestésicos exclusivamente por vía intravenosa, basándose en la combinación de diferentes fármacos para realizar la inducción y el mantenimiento anestésico; esto con el objetivo de proporcionar analgesia, pérdida de la conciencia, amnesia y relajación muscular, con mínimas alteraciones fisiológicas (Clarke et al., 2014; White, 2015; Queiroz-castro et al., 2006; Beths, 2017). Esta técnica es empleada principalmente cuando la anestesia inhalatoria no es posible o no se indica (Beths, 2017).

Los fármacos, más utilizados para TIVA en medicina veterinaria son propofol, alfaxalona y ketamina. Así mismo, se emplean fármacos adyuvantes como opioides, agonistas de adrenoceptores α2 o lidocaína para disminuir los efectos secundarios potenciales de estos, proporcionando estabilidad cardiovascular, relajación muscular, analgesia y/o una disminución en los requerimientos anestésicos de estos (White, 2015; Beths, 2017). La TIVA gradualmente se ha popularizado en la práctica veterinaria y su investigación en cabras se ha hecho cada vez más notoria en los últimos años (Doherty et al., 2007; Dzikiti et al., 2009; Dzikiti et al., 2010; Dzikiti, 2013; Ferreira et al., 2016; Vieitez et al., 2017). Hoy en día la información sobre los protocolos TIVA aplicables en cabras es muy escasa (Dzikiti, 2013). Siendo el propofol, el agente más adecuado para esta técnica anestésica, ya que tiene un gran volumen de distribución, rápida biotransformación y tasa de aclaramiento (Bettschart Wolfensberger et al., 2000). Lin et al. en 1997, reportaron que la TIVA con propofol provoca mejores y más rápidas recuperaciones, cuando se compara con agentes disociativos como la ketamina en el ganado ovino. No obstante, sus pobres propiedades analgésicas lo hacen insatisfactorio como agente único, ya que las dosis requeridas para eliminar las respuestas a estímulos quirúrgicos provocan una depresión cardiopulmonar significativa (Smith et al., 1994), por lo que, debe considerarse su combinación con otros fármacos para realizar procedimientos dolorosos (Langley y Heel, 1988; Sneyd, 2004; Beths, 2008). Larenza et al. (2005) informaron que su uso en infusión continua en combinación con ketamina causa inmovilidad y efectos cardiopulmonares comparables con la anestesia con sevoflurano. A su vez, Dzikiti et al. (2010), informó que la administración conjunta de propofol (0.2 mg kg^{-1} $minuto^{-1)}$ y fentanilo (0.02 mg kg^{-1} $hora^{-1}$) o midazolam (0.3 mg kg^{-1} $hora^{-1}$), para la inducción y el mantenimiento de la anestesia en cabras, da como resultado una anestesia satisfactoria, y un adecuado mantenimiento de los parámetros cardiopulmonares, sin embargo, menciona que las recuperaciones con la combinación de fentanilo-propofol podrían ser de mala calidad. Recientemente, Vieitez et al. (2017), mencionaron que la asociación infusión de propofol (0.2 mg kg^{-1} $minuto^{-1}$), junto con la administración de una IC de lidocaína (50 μg kg^{-1} $minuto^{-1}$), midazolam (0.15 mg kg^{-1} $hora^{-1}$) y fentanilo (6 μg kg^{-1} $hora^{-1}$) en cabras sometidas a craneotomía, da lugar a una anestesia satisfactoria con un impacto mínimo en la función cardiopulmonar, así como una adecuada recuperación

anestésica. Hoy en día se busca una anestesia que sea segura, que produzca mínimos cambios hemodinámicos, que otorgue adecuada analgesia, con una biotransformación y una tasa de eliminación rápida; y que proporcione una recuperación adecuada y estable. Hasta ahora no existe un tipo de anestesia que reúna estas características, sin embargo, la TIVA, cumple muchos de esos criterios (White, 1983; Dzikiti, 2013; Beths, 2017).

3. HIPÓTESIS

I. El empleo del protocolo PIVA (isoflurano inhalatorio con la infusión continua de lidocaína, ketamina y fentanilo) y TIVA (Infusión continua de propofol, lidocaína, ketamina y fentanilo), producirán un adecuado plano anestésico, con suficiente analgesia y estabilidad cardiopulmonar, así como una recuperación anestésica de buena calidad en caprinos sometidos a abomasotomía.

4. OBJETIVOS

4.1. Objetivo General:

Comparar el efecto anestésico, analgésico, cardiopulmonar y conductual de la infusión constante de fentanilo-lidocaína-ketamina en cabras anestesiadas con propofol o isoflurano y sometidas a abomasotomía electiva.

4.1.1. Objetivos Específicos:

- Comparar los tiempos anestésicos: latencia, plano anestésico quirúrgico y en la recuperación de los protocolos TIVA y PIVA.

- Comparar el efecto en las variables cardiopulmonares: Frecuencia cardiaca, frecuencia respiratoria, la presión arterial sistólica, diastólica y media (PAS, PAD y PAM respectivamente) de manera invasiva, saturación parcial de oxígeno de la hemoglobina (SpO_2), CO_2 expirado (Et CO_2), presión parcial de oxígeno (PaO_2), presión parcial de dióxido de carbono ($PaCO_2$) entre el protocolo PIVA y TIVA.

- Comparar la calidad de recuperación anestésica entre los protocolos PIVA y TIVA.

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6. ARTÍCULO

Este artículo fue enviado y elaborado acorde con las normas editoriales de la revista Veterinary Anaesthesia and Analgesia.

6.1. Correo del editor.

Veterinary Anaesthesia and Analgesia <onbehalfof@manuscriptcentral.com>
Lun 04/06/2018, 01:22 AM
p.ivette.velazquez@hotmail.com

04-Jun-2018

Dear Dr. Velazquez-Delgado,

A manuscript entitled Anaesthetic effects of fentanyl- lidocaine-ketamine infusion in propofol- or isoflurane-anaesthetized goats undergoing abomasotomy (VAA-18-0143) has been submitted by Dr. Perla Velazquez-Delgado to Veterinary Anaesthesia and Analgesia.

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Submitted to	Veterinary Anaesthesia and Analgesia
Manuscript ID	VAA-18-0143
Title	Anaesthetic effects of fentanyl- lidocaine-ketamine infusion in propofol- or isoflurane-anaesthetized goats undergoing abomasotomy
Authors	Velazquez-Delgado, Perla GUTIERREZ-BLANCO, EDUARDO Torres-Acosta, Juan Felipe de Jesus Ortega-Pacheco, Antonio Aguilar-Caballero, Armando Dzikiti, Brighton
Date Submitted	04-Jun-2018

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Anaesthetic effects of fentanyl- lidocaine-ketamine infusion in propofol- or isoflurane-anaesthetized goats undergoing abomasotomy

Perla Velazquez-Delgado[a], Eduardo Gutierrez-Blanco[a], Felipe Torres-Acosta[a], Antonio Ortega-Pacheco[a], Armando Aguilar-Caballero[a], Brighton Dzikiti[b]

[a] Department of Animal Health and Preventive Medicine, Universidad Autonoma de Yucatan, Merida, Yucatan, Mexico

[b] Department of Large Animal Clinical Science, School of Veterinary Medicine, Ross University, Basseterre, St. Kitts, West Indies, St. Kitts & Nevis

Correspondence: **Eduardo Gutierrez-Blanco, Department of Animal Health and Preventive Medicine, Section of Anesthesia and Pain Management, Faculty of Veterinary Medicine, Autonomous University of Yucatan, Km 15.5 road Merida-Xmatkuil, Merida, Yucatan 97000, Mexico. E-mail: gublan@correo.uady.mx**

Running head: Balanced anaesthesia in goats

Author's contributions:

[1]PV: data management, data interpretation, statistical analysis and preparation of manuscript

[2]EG: study design, data management, data interpretation and preparation of manuscript

[3]FT: surgery, data interpretation, statistical analysis and preparation of manuscript

[4]AO: surgery, data management and preparation of manuscript

[5]AA: data management, and preparation of manuscript

[6]BD: study design, data interpretation and preparation of manuscript

Acknowledgements: Perla Velazquez-Delgado was sponsored by a MSc scholarship provided by CONACYT, Mexico and the basic science project CB-2013-01221608.

Conflict of interest statement: "The authors declare no conflict of interest".

280 words

Abstract

Objective. To compare the anaesthetic, analgesic, cardiopulmonary and behavioural effects of a constant rate infusion of fentanyl- lidocaine-ketamine in propofol- or isoflurane-anaesthetized goats undergoing abomasotomy.

Study design. A prospective non-blinded clinical study

Animals. Eighteen goats

Methods

All the goats were premedicated with fentanyl (10 μg kg^{-1}), lidocaine (2 mg kg^{-1}) and ketamine (1.5 mg kg^{-1}) administered intravenously. Anaesthesia was induced with propofol. The goats were randomly assigned to either total intravenous anaesthesia (TIVA) or partial intravenous anaesthesia (PIVA) group for maintenance of anaesthesia which consisted of fentanyl (10 μg kg^{-1} $hour^{-1}$), lidocaine (50 μg kg^{-1} $minute^{-1}$) and ketamine (50 μg kg^{-1} $minute^{-1}$) as constant rate infusion (CRI), in addition, to CRI of propofol at 0.3 mg kg^{-1} $minute^{-1}$ (TIVA group) or isoflurane vaporized in oxygen with initial end-tidal (FE′Iso) concentration of 1.2% (PIVA group). Anaesthetic administration rate was adjusted intermittently according to assessed signs of anaesthetic depth. Cardiopulmonary parameters, arterial blood-gas

analysis, FE′Iso and the CRI rates were recorded intermittently. Anaesthetic recovery was timed, and quality scored. Data were analysed using ANOVA ($p < 0.05$).

Results

The mean propofol dose for anaesthetic maintenance was 0.44 ± 0.07 mg kg^{-1} $minute^{-1}$ in TIVA, while the mean FE′Iso requirements were 0.81 ± 0.2 in PIVA. Cardiopulmonary function was minimally-affected in both groups. Duration of recovery from anaesthesia was similar in both groups. Quality of recovery was uneventful in group PIVA, while some abnormal behavioural signs were observed in group TIVA.

Conclusions and clinical relevance

At the doses administered, fentanyl- lidocaine-ketamine infusion combined with either propofol or isoflurane, produced satisfactory surgical anaesthesia with minimal changes on cardiopulmonary functions. However, recoveries after the combination of propofol-fentanyl-lidocaine-ketamine are of poor quality.

Keywords: anaesthesia total intravenous, anaesthesia partial intravenous, goats, constant rate infusion.

431 words

Introduction

Goats are increasingly being used as surgical models in animal experiments (Larenza et al. 2005) and therefore need to be submitted to general anaesthesia. Commonly, anaesthesia is

maintained by inhalation agents, using injectable anaesthetic drugs for induction or anaesthetic maintenance (Reid et al. 1993). If anaesthesia is maintained exclusively with a single inhalation agent, high doses are required to achieve an adequate anaesthetic level, increasing the likelihood of adverse effects (Steffey Mama 2007). In current anaesthetic practice there is no single ideal anaesthetic agent, although some have advantages in certain areas, they lack other important ideal properties. A balanced anaesthesia can be achieved using a combination of different drugs (Tonner 2005). Recent studies in goats have proposed the use of various drugs for this purpose. An alternative is the combination of inhalation anaesthetics with intravenous drugs (analgesics and/or sedatives), known as partial intravenous anaesthesia (PIVA) (Doherty et al. 2002; Doherty et al. 2004; Doherty et al. 2007; Dzikiti et al. 2011a; Dzikiti et al. 2011b; Dzikiti et al. 2011c), which leads to an improvement in cardiopulmonary parameters due to the reduction in the requirements of inhalation anaesthetic agents and their dose-related cardiovascular depressing effects (Fujita et al. 1993; Aida et al. 1996; Galloway et al. 2004; Funes et al. 2014). General anaesthesia can also be maintained by means of total intravenous anaesthesia (TIVA) as an alternative to inhalation anaesthetics (Beths 2017). Propofol has proven to be the most suitable agent for TIVA protocols (Dzikiti 2013; Beths 2017) due to its pharmacokinetic properties that allow rapid onset, ultra-short action and rapid recovery (Bettschart-Wolfensberger et al., Beths 2017). However, its poor analgesic properties make it unsatisfactory as a single agent (Smith et al. 1994; Bettschart-Wolfensberger et al. 2000), therefore its combination with other analgesic drugs during painful procedures should be considered (Langley & Heel 1988; Sneyd 2004; Beths 2008). Various drugs have been used for this purpose (Carroll et al. 1998; Dzikiti et al. 2009; Kumar et al. 2014; Larenza et al. 2005; Vieitez et al. 2017). Several

studies have reported the effects of fentanyl, lidocaine and ketamine or the combination of lidocaine and ketamine constant rate infusions on isoflurane (Doherty et al. 2007; Dzikiti et al. 2011b) or propofol (Larenza et al. 2005; Dzikiti et al. 2010; Vieitez et al. 2017) requirements. Current literature lacks descriptions of sedative and sparing effects of lidocaine, ketamine and fentanyl drug combination in goats undergoing surgery.

Then the aim of this study was compare the anaesthetic, analgesic, cardiopulmonary and behavioural effects of a constant rate infusion of fentanyl- lidocaine-ketamine in propofol- or isoflurane-anaesthetized goats undergoing abomasotomy.

Materials and methods

The study protocol was approved by the Research Ethics committee of the Faculty of Veterinary Medicine and Animal Science of the Autonomous University of Yucatan (Protocol number CB-CCBA-M-2017-001).

Animals

Eighteen mature female Criollo does (3-5 years old), weighing 28-41 kg (CC (2/3), were used in the present study. The goats were healthy based on physical examination, complete blood count (CBC) and serum biochemical analyses. The does were submitted to surgery as a part of a different study.

Anaesthetic procedure and Study Design

Food and water were withheld for 24 hours before anaesthesia. Baseline measurements for heart rate (HR), respiratory rate (f_R), rectal temperature, and non-invasive arterial blood pressure were recorded fifteen minutes before induction of anaesthesia in the housing pen.

An 18-gauge catheter was inserted into the left jugular vein for administration of intravenous (IV) fluids. A 22- gauge catheter was inserted into the auricular artery to facilitate measurement of arterial blood pressures and for the collection of arterial blood samples for gas analyses.

Fentanyl was administered manually at a dose of 10 μg kg ^{1} IV over a 1-minute period. Two minutes later, the degree of sedation was evaluated according to the modified scale described by Grint et al. (2009). Lidocaine (2 mg kg^{-1}) was then administered IV over a 1-minute period and sedation was re-assessed two minutes later. Thereafter a bolus of ketamine (1.5 mg kg^{-1}) was administered IV over a 1-minute period, reassessing sedation two minutes later as above mentioned. Immediately before induction of anaesthesia, the goats were pre-oxygenated (100% oxygen) for three minutes by face mask at a flow rate of 5 L $minute^{-1}$.

General anaesthesia was induced with propofol (3 mg kg-^{1} to effect) (Propofol 1%; Fresenius Kabi, Austria) IV over 30 seconds. Immediately after induction, the goats were connected to a circle re-breathing system (Multiplus MEVD; Royal Medical Co. Ltd., South Korea) with an initial oxygen flow rate of 50 mL kg-^{1} minute-^{1}. The goats were allocated in one of the two groups by means of a computer-generated random numbers (QuickCalcs GraphPad Software; www.graphpad.com/quickcalcs/randomize1/), then drugs for maintenance of anaesthesia were administered as follows:

- TIVA group: Constant rate infusions (CRIs) of propofol (Propofol 1%; Fresenius Kabi, Austria) at 0.3 mg kg $^{-1}$ minute $^{-1}$; fentanyl (Fenodid; Pisa Farmaceutica, Mexico) at 10 μg kg^{-1} $hour^{-1}$; ketamine (Anesket;Pisa Farmaceutica, Mexico) at 50 μg kg^{-1} $minute^{-1}$ and lidocaine (Pisacaina 2%; Pisa Farmaceutica, Mexico) at 50 μg kg $^{-1}$ $minute^{-1}$. The propofol infusion rate was adjusted to maintain surgical anaesthesia as described later.

- PIVA group: CRIs of fentanyl at 10 μg kg^{-1} $hour^{-1}$; ketamine at 50 μg kg^{-1} $minute^{-1}$ of and lidocaine at 50 μg kg^{-1} $minute^{-1}$ in addition to isoflurane vaporized in oxygen at an FE′Iso of 1.2% and oxygen flow rate of 100 mL kg^{-1} $minute^{-1}$ for the first 10 minutes and 50 mL kg^{-1} $minute^{-1}$ thereafter. The isoflurane administration rate was adjusted to maintain surgical anaesthesia as described later.

Propofol was administered by an infusion pump device (Colleague 3: Baxter, IN, USA). Exception for propofol in both groups, drugs for CRI were diluted to 50 mL with sterile water and administered by an infusion pump device (Colleague 3: Baxter, IN, USA), and their infusion started immediately after completion of administration of the last bolus of propofol for induction of general anaesthesia. Saline 0.9% (Solucion CS; Pisa Farmaceutica, Mexico) was administered at 5 mL kg^{-1} $hour^{-1}$ throughout anaesthesia using an infusion pump device (Colleague 3: Baxter, IN, USA).

Cardio-respiratory variables measurement

Heart rate (HR) and rhythm were obtained from a continuous lead II ECG recording. Systolic, mean and diastolic arterial blood pressures (SAP, MAP and DAP, respectively) were continuously measured from the right auricular artery using a multiparameter monitor (PM9000-Vet, Mindray China), which was connected to a heparinized saline line tube that was attached to an electronic pressure transducer (Safsure, Mindray China), zeroed to barometric pressure and adjusted to the heart level while the goat was in dorsal recumbence. Haemoglobin oxygen saturation (SpO_2) was monitored with a pulse oximeter (PM9000-Vet, Mindray China) with a transmittance probe that was placed on the tongue. The f_R was obtained from the capnogram. Rectal temperature was recorded with a digital thermometer

and was targeted to be maintained between 38.5 and 39.5 ºC using a thermal warming blanket (HP300-A; HoMedics, China).

Cardio-respiratory variables including HR, SAP, DAP, MAP, f_R and body temperature were recorded during anaesthetic induction and every 5 minutes during the maintenance of anaesthesia.

Arterial blood samples for gas analyses were collected in 2-mL heparinized syringes, prior to premedication with fentanyl, lidocaine and ketamine (baseline), at 15, 30 minutes after surgery started and 10 minutes after extubation. The samples were analysed for oxygen tension (PaO_2), carbon dioxide tension ($PaCO_2$), and hydrogen ion concentration negative (pH), bicarbonate ion concentration (HCO_3), glucose and lactate concentrations within 5 minutes of collection using a pre-calibrated blood gas analyzer (i15Vet Edan China).

Evaluation of anaesthetic depth.

To maintain surgical anaesthesia, the rate of delivery of propofol (TIVA) or isoflurane (PIVA) was always adjusted by the same anaesthetist (PV) to ensure the following clinical signs: the absence of palpebral reflex, ventro-medial eye rotation, loss of mandibular and neck muscle tone, absence of purposeful movement in response to surgical stimulation, and minimal changes in the autonomic response (+/- 20% variation from baseline values of HR and MAP).

Monitoring, time points and adjustment of vaporizer settings

The inspired and end-tidal isoflurane (PIVA group only) and expired CO_2 concentrations (FIIso, FE'Iso and PE'CO_2, respectively) were also measured with an infrared gas-anaesthetic agent analyser and capnometer, respectively included in the multiparameter

monitor through a side stream sampling line connected to the proximal end of the ET tube. The gas analyser was calibrated before each anaesthetic procedure.

The goats were allowed to breathe spontaneously throughout the procedure unless PE'CO_2 values rose above 60 mmHg for a period of more than 5 minutes; in which case, mechanical ventilation was started to maintain eucapnia (35-45 mmHg PE'CO_2).

For TIVA group, if MAP or HR increased by > 20% from baseline, then the surgery was interrupted and a propofol bolus of 1 mg kg^{-1}over a 30 second period administered IV, and the propofol CRI increased by 0.08 mg kg^{-1} $minute^{-1}$ until HR and MAP returned to within 20% of normal baseline values. Conversely, if MAP decreased > 20% of baseline values, then the propofol CRI decreased by 0.08 mg kg^{-1} $minute^{-1}$ or less until HR and MAP returned to previously recorded values. If MAP decreased below 60 mmHg, then a bolus of 5 ml kg^{-1} of isotonic saline (NaCl 0.9%) was administered IV as rapidly as possible.

For PIVA group, if MAP or HR increased > 20% of baseline values, then the surgery was stopped and the FE'ISO increased by 0.2% units or more until HR and MAP returned to a previously recorded value. Conversely, if MAP decreased > 20% of baseline values, then the FE'ISO was decreased by 0.2% units or more until HR and MAP returned to previously recorded values. If MAP decreased to 60 mmHg or less, 0.9% saline at 5 mL kg^{-1} was infused over 15 minutes.

Surgical procedure

Surgery started 45 minutes after the beginning of CRIs and completion of instrumentation. All surgeries were performed through a paramedian incision by the same surgeons (AOP/EBR), using the technique described by Hendrickson & Baird (2013). Data were recorded immediately at the beginning of the skin incision (T0, baseline), immediately after

laparotomy (T1), during traction and exteriorization of the abomasum (T2), during abomasotomy (T3), at the midpoint of closure of the abomasum (T4), at the midpoint of closure of the abdominal wall (T5), during closure of the subcutaneous tissue (T6) and at the midpoint of the closure of the skin (T7).

Surgery time (time from the first incision until the placement of the last suture), anaesthesia time (time from injection of propofol to turning off the vaporizer or infuser pump), and time to extubation (time elapsed from turning off the vaporizer dial or infuser pump until extubation) were recorded. Goats were disconnected from the rebreathing circuit at extubation time which was adjudged by the return of the swallowing reflex. Time to first head lift, time to attainment of sternal recumbency (time elapsed from turning off the vaporizer or infuser pump until sternal recumbency), and time to standing (time elapsed from turning off the vaporizer or infuser flow until standing and defined as ability to stay standing at least 10 seconds without assistance) were recorded.

Post-anaesthetic sedation and recovery.

Sedation during recovery was assessed every hour for up to 4 hours after extubation according to the modified scale described by Grint et al. (2009). Quality of recovery from anaesthesia was scored using a modified scale described by Carroll et al. (1998). After the last sedation assessment, all the goats were returned to their hosing pen and then an intramuscular dose of meloxicam (0.3 mg kg) was administered every 24 hours for 3 consecutive days.

Statistical analysis

Data were analysed by using a Statistical software package (Graphpad Software 5.0, CA, USA). A Shapiro-Wilk test test was used to test data for distribution patterns. Non-parametric and ordinal variables are expressed as median and range. Within each group, changes in sedation scores, and quality data with time were analysed using Friedman test followed by Dunn's multiple comparison test, respectively, when a significant difference was detected. Differences in nonparametric data between groups were analysed using Mann-Whitney test. Parametric data are expressed as mean ± standard deviation (SD). Physiological data (HR, SAP, DAP, MAP, body temperature, f_R) and blood–gas and analyte data (PaO_2 – $PaCO_2$, HCO_3, Lactate, pH, glucose) were tested for statistically significant differences overtime using ANOVA for repeated measures followed by Dunnett′s test when appropriate. Paired t tests was used for comparisons between groups at each time point and for the values of anaesthesia time, surgery time, time to first head lift, time to accomplish sternal recumbency and time to standing. Differences were considered significant at $p < 0.05$.

Results

All the goats became heavily sedated following administration of fentanyl, lidocaine and ketamine. Sedation scores were 10 (6-14) and 10 (7-17) for–PIVA and TIVA groups, respectively ($p > 0.05$). In both groups, all goats showed abnormal behavioural signs such as exaggerated tail-wagging, chewing movements and restlessness (Table 1) after fentanyl premedication but before induction. Mean propofol doses for induction of anaesthesia were similar (3.9 mg kg^{-1}) for both groups.

Cardio-respiratory variables

The cardio-respiratory variables did not differ significantly between groups (Tables 2 and 3), except for SAP at surgical times T3, T5 and T6, for which significantly higher values were observed during TIVA ($p = 0.0382$, 0.0398 and 0.0143, respectively). The rectal temperature was maintained within the pre-determined range (38.5–39.5 C) and there were no statistically significant differences between or within groups; and the arterial blood gases and analytes data did not differ significantly between groups.

Anaesthetic requirements

The observed mean FE′Iso–was 0.81±0.20% (range: 0.54 – 1.12%) and the mean CRI of propofol was 0.40±0.6 mg kg^{-1} $minute^{-1}$ (range: 0.290–0.570 mg kg^{-1} $minute^{-1}$), during the surgical procedure (Table 4). There were no statistical differences within any group for anaesthetic requirements from T0 to T6.

Anaesthesia recovery

There were no significant differences between treatment groups in times to extubation, sternal position and standing position (Table 5). The scores for quality of recovery from anaesthesia were significantly lower in PIVA 2 (1-7) than in TIVA 8 (0-13). The goats of TIVA group showed abnormal behavioural signs such as exaggerated tail-wagging, vocalizations, restlessness, ear motions and leaning on objects during recovery (Table 6). In terms of recovery times (Table 5), these were similar for both groups.

Discussion

The use of pre-anaesthetic drugs in ruminants has been shown to minimize stress that may be caused by handling and containment, facilitating the anaesthetic induction process and reducing anaesthetic requirements. This minimizes the possibility of adverse effects, provides preventive analgesia and improves quality of recovery from anaesthesia (Valverde & Doherty 2008; Lin 2014).

Current literature lacks descriptions of sedative effects of the combination of lidocaine, ketamine and fentanyl in goats. In 2010, Dzikiti et al. reported that premedication with fentanyl at a dose of 0.02 mg kg^{-1} caused deep sedation (the goats went into–lateral recumbency and were unable to lift their heads), which was similar to the level of sedation recorded in the goats of the present study. Tallarida (2002) and Hendrickx et al. (2008), reported that combinations of two or more drugs may generate interactions categorized as "synergistic", "additive" or "infra-additive" when their combined effect exceeds, equals or is less than that of the total of the effects of the individual drugs, respectively. In the present study, we used three different drugs that were administered simultaneously, and with different mechanisms of action: (1) fentanyl is a pure opioid agonist of the receptors μ, which modulates the impulses from the peripheral nerves before they are transmitted to the superior centers (Wagner et al. 2002; Steagall et al. 2006), (2) lidocaine is a local anaesthetic belonging to the amide group, a non-selective blocker of sodium channels (Thomas et al. 2004; Webb & Pablo 2009; Frölich et al. 2010), while (3) ketamine is a dissociative anaesthetic and N-methyl-D-aspartate receptor antagonist (NMDA) which prevents the binding of the excitatory neurotransmitter glutamate, resulting in a depression of the activity of the thalamocortical, limbic and reticular activated systems (Prassinos et al. 2005; Pozzi et

al. 2006). We therefore hypothesize that the combination of these three drugs may generate an additive effect, as mentioned by Tallarida, (2002) and Hendrickx et al. (2008). This would explain the similar response in the sedation of goats observed in the present study despite administration of half the dose of fentanyl used by Dzikiti et al. (2010) but adding two more drugs (ketamine and lidocaine).

Several studies have shown behavioural changes associated with the administration of opioids in ruminants, due to central nervous system (CNS) stimulation (Branson et al. 2001; Valverde & Doherty 2008; Lin 2014), producing an increase in vocalization and agitation (Carroll et al. 1999), chewing movements and nystagmus (Upton et al. 2003), as well as excessive tail wagging (Dzikiti et al. 2011b); these findings concur with those observed in the present study (Table 1) during anaesthetic premedication with fentanyl. However, such effects are not common when opioids are co-administered with a sedative or when administer in animals with pain (Lin 2014). This may explain the observation of less pronounced excitatory behavioural effects in the present study wherein fentanyl was co-administered with lidocaine and ketamine.

As mentioned above, the use of sedative drugs facilitates restraint during the anaesthetic induction process and reduces induction and maintenance drug requirements (Lin 2014). The use of propofol and its suitability for anaesthetic induction in goats as well as effective induction doses in goats have been previously reported (Nolan & Reid 1991; Reid et al. 1993; Pablo et al. 1997; Carroll et al. 1998; Dzikiti et al. 2009). Studies in non-premedicated goats, have reported induction doses of 5.1 mg kg^{-1} (Pablo et al. 1997) and 5.3 mg kg^{-1} (Dzikiti et al. 2009). In 2010, Dzikiti et al. reported a propofol induction dose of 4 mg kg^{-1} in goats premedicated IV with fentanyl (0.02 mg kg^{-1}) or midazolam (0.3 mg kg^{-1}). The propofol

induction dose in the present study (3.9 mg kg^{-1}) was similar to that reported by Dzikiti et al. in 2010; although the dose of fentanyl used as a premedication by this author was twice that used in this study. That similar propofol induction doses were observed and could be explained by the possible additive effect from co-administration of fentanyl with lidocaine and ketamine in the present study. There are other factors that can influence induction doses; one being the temperament of the goats. Lower induction doses (3.0 mg kg^{-1}) have been reported in pet goats which are expected to be docile or accustomed to handling by humans (Pablo et al. 1997; Prassinos et al. 2005). That goats included in this study did not have a period of adaptation and were anaesthetized for their first time at the moment of the abomasotomy and this could explain the slightly higher induction dose in comparison to that observed by Pablo et al. 1997 and Prassinos et al. 2005. A propofol-associated adverse effect during induction of anaesthesia; myoclonus, reported in some previous studies (Pablo et al. 1997; Bettschart-Wolfensberger et al. 2000; Dzikiti et al. 2009) was not observed in the present study.

The mean propofol infusion rate observed for maintenance of anaesthesia in present study (0.44 mg kg^{-1} $minute^{-1}$) is higher than those previously reported in premedicated goats. Larenza et al. (2005) and Dzikiti et al. (2010) reported propofol infusion rates of 0.2 and 0.3 mg kg^{-1} $minute^{-1}$ respectively. Both studies administered fentanyl (0.02 mg kg^{-1} $hour^{-1}$) midazolam (0.3 mg kg^{-1} $hour^{-1}$) (Dzikiti et al. 2010) and ketamine (0.03 mg kg-^{1} $minute^{-1}$) (Larenza et al. 2005), which reduced the rate of propofol infusion required to maintain anaesthesia. Minimal infusion rate (MRI) as in MAC studies, entails anaesthesia in 50% of patients exposed to a standardized noxious stimulus (Mannarino et al. 2012). However, variations in the type of stimulus may have a profound effect on the observed rate of infusion

(Eger et al. 1988; Ferreira et al. 2016), so surgical stimulation may exceed the standardized supramaximal stimulus applied in these studies, resulting in a relatively higher infusion rate (Ferreira et al. 2016). Like MAC, CRI is influenced by the pharmacokinetic properties of anaesthetic drugs, the patient's age and physical condition, as well as their co-administration with other drugs (opioids and/or sedatives) and the patient's anaesthetic requirements (Kaul & Bharti 2002). Recently, Vieitez et al. 2017, reported a lower propofol infusion rate of 0.2 mg kg^{-1} $minute^{-1}$during co-administration of a lidocaine CI (50 µg kg^{-1} $minute^{-1}$), midazolam (0.15 mg kg^{-1} $hour^{-1}$) and fentanyl (6 µg kg^{-1} $hour^{-1}$) in goats undergoing craniotomy. However, the difference in pain associated with the type of surgical intervention, where abomasotomy is categorized as a moderate to very painful intervention, compared to craniotomy (Carroll 1998; Mathews 2000) should be considered, this may explain the higher infusion rate observed in the present study when compared to the Vieitez study.

Studies by different authors have reported MAC values of isoflurane in goats ranging from 1.23 (Antognini & Eisele 1993) to 1.29 (Hikasa et al. 1998) and 1.50% (Doherty et al. 2002). Comparatively, the mean FE′Iso observed in the present study (0.81%) is much lower. The difference in the observed isoflurane requirements may be explained by the possible additive effect of the combination of the three drugs used in the present study as observed in dogs (Aguado et al. 2010) where a reduction up to 97% in isoflurane requirements with lidocaine, ketamine and fentanyl drug combination, were observed in bitches undergoing ovariohysterectomy.

The significant increases from baseline values observed over time in cardiovascular values (Table 2) could be due to the surgical stimulation and activation of the autonomic (sympathetic) nervous system during traction and exteriorization of the abomasum (T2) and

its reinsertion (T4). However, when comparing between groups, the values of systolic blood pressure (SAP) were significantly lower in PIVA when comparing to TIVA at T3, T5 and T6 during surgery. This may be explained by the fact that isoflurane reduces vascular resistance secondary to vasodilatation by decreased activity of the autonomic (sympathetic) nervous system thereby causing a decrease in blood pressure (Hikasa et al. 1998). However, the SAP values in PIVA group were never lower than those obtained at baseline or even just before surgery started.

Quality of recovery from anaesthesia in the PIVA group was characterized by a smooth and uneventful recovery, agreeing with what was observed by Dzikiti et al. in 2011b, where they reported that general behaviour of goats anaesthetized with isoflurane and fentanyl to be acceptable at all times during recovery, with no observed abnormal behaviour. It is also known that anaesthetic recovery from isoflurane is expected to be rapid in goats (Antognini & Eisele 1993; Dzikiti et al. 2011b), especially when used in low concentrations as in the present study. On the other hand, in the TIVA group, the quality of recovery was characterized by abnormal behavioural signs in most goats, with a higher degree of ataxia than in PIVA group, resulting in a higher number of attempts to standing and a higher range in recovery times as mentioned above. Currently, there is no literature on quality of anaesthetic recovery from TIVA with propofol, fentanyl, lidocaine and ketamine in goats. The presence of these behavioural changes is associated to the administration of opioids (Branson et al. 2001; Valverde & Doherty 2008; Lin 2014); consistent with what was reported by Dzikiti et al. (2010) who caution that care should be taken during recovery from anaesthesia obtained from a combination of propofol and fentanyl since excitatory behavioural signs may be expected. Therefore, stopping fentanyl infusion earlier may

minimize occurrence of excitatory effects (Dzikiti et al. 2010) during recovery from anaesthesia.

Conclusion and clinical relevance

At the doses administered, constant rate infusions of fentanyl- lidocaine-ketamine combined with either propofol or isoflurane produced a satisfactory quality of anaesthesia during surgery with minimal changes on cardiopulmonary function. However, recoveries after the combination of propofol-fentanyl- lidocaine-ketamine are of poor quality.

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Table 1 Proportion (%) of goats displaying specified behavioural responses following premedication with fentanyl (10 μg kg^{-1}), lidocaine (2 mg kg^{-1}) and ketamine (1.5 mg kg^{-1}) in goats.

Treatment	Behavioural reactions					
	Fentanyl	**%**	**Lidocaine**	**%**	**Ketamine**	**%**
PIVA	Chewing movements	55.5	Chewing movements	33.3	Chewing movements	22.2
	Exaggerated tail-wagging	33.3			Nystagmus	33.3
	Vocalization	11.1				
	Exaggerated ear movement	11.1				
	Miosis	11.1				
TIVA	Chewing movements	66.6	Chewing movements	33.3	Chewing movements	22.2
	Exaggerated tail-wagging	22.2			Exaggerated tail-wagging	11.1
	Vocalization	22.2			Nystagmus	22.2
	Exaggerated ear movement	11.1				
	Miosis	11.1				

Table 2 Cardiopulmonary variables (mean ± DS) observed in goats undergoing abomasotomy and receiving continuous infusion of fentanyl (10 μg kg^{-1} $hour^{-1}$), lidocaine (50 μg kg^{-1} min^{-1}) and ketamine (50 μg kg^{-1} min^{-1}) in conjunction with isoflurane (PIVA) or continuous infusion of propofol (TIVA) for anaesthetic maintenance.

Variables	Treatment	Time points								
		Baseline	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**
HR	TIVA	70±9.4	65±19.7	69±17.5	78±16.1†	75±18.1	77±20.2†	80±17.7†	79±17.4†	76±17.6†
	PIVA	66±9.9	84±19.3*	86±18.9*	88±15.6*	92±16.1*	95±18.6*†	89±21*	88±18.7*	88±17.5*
F_R	TIVA	21±5.0	11±4.8*	12±5.4*	16±6.8*	12±4.1*	14±4.8*	12±4.7*	15±6.6*	15±5.7*
	PIVA	21±5.3	10±3.1*	9±3.50*	12±5.8*	11±3.2*	11±4.4*	10±4.2*	11±5.8*	14±6*†
SaO_2	TIVA	98±1.8	97±2.6	97±2	96±2.9	97±1.4	97±2.1	98±0.9	98±1	98±0.8
	PIVA	96±2.3	97±1.2	97±1.5	97±1.5	97±1.8	97±2.1	97±1.8	98±0.7	98±0.7
$EtCO_2$ (mmHg)	TIVA	41.3±2.8	40.3±3.5	41.3±4.6	41±5.8	42.3±4.5	40.5±5.5	40.4±5.1	39.7±3.5	39.4±4
	PIVA	42±2.6	40.7±5.2	40.7±5.7	41.2±8.1	40.6±4.2	40±7.4	41±6.3	38.2±4.7	35.8±6.5
SAP (mmHg)	TIVA	134±24.5	98±7.7*	109±8.9*†	129±15†	118±14.4a*†	110±10*†	119±10.8a*†	114±6.4a*†	110±7.6*†
	PIVA	137±26.2	97±10.8*	104±12*	124±21.3†	105±9.4b*	104±12.8*	107±12.4b*	103±10.2b*	107±12.5*
DAP (mmHg)	TIVA	85±25.3	72±12.7*	81.5±11.6†	99±12.4*†	88±12.3†	84±12†	95±9.8†	87±8.9†	85±9.2†
	PIVA	94±21.3	73±7.8*	78±10.6*	94±17.5†	81±11.3*	80±13.9*	84±13.2†	81±11.7*	86±11.1†
MAP (mmHg)	TIVA	102±22.7	80±11.3*	90±10.1†	108±12.5†	96±13.9†	92±11.3†	101±9.6†	97±8.5†	93±8.4†
	PIVA	100±10	80±10.7*	86±10.1*	104±18.6†	88±10.6*	89±12.6*	91±12.3†	89±10.2*	92±12.1*†

* significantly different within the same group compared to baseline. † significantly different within the same group compared to the value of T0. a, b significantly different between groups ($p < 0.05$).

Table 3. pH and blood gas values (mean ± DS) observed in goats undergoing abomasotomy and receiving continuous infusion of fentanyl (10 μg kg^{-1} $hour^{-1}$), lidocaine (50 μg kg^{-1} $minute^{-1}$) and ketamine (50 μg kg^{-1} $minute^{-1}$) in conjunction with isoflurane (PIVA) or continuous infusion of propofol (TIVA) for anaesthetic maintenance.

Variable	Treatment	Baseline	15	30	POST
pH	TIVA	7.529 ± 0.03	7.36 ± 0.04*	7.38 ± 0.04 *	7.449 ± 0.05
	PIVA	7.498 ± 0.01	7.378 ± 0.03	7.393 ± 0.08	7.466 ± 0.04
PaO_2 (mmHg)	TIVA	84.3 ± 4.04	493.7 ± 177.8 *	522 ± 129.6 *	98 ± 4.35
	PIVA	88 ± 2.6	502.7 ± 12.64*	582.3 ± 100.1 *	95.67 ± 7.23
$PaCO_2$ (mmHg)	TIVA	37.6 ± 2.17	46.8 ± 1.01*	44.63 ± 1.38*	39.4 ± 1.38
	PIVA	37.83 ± 6.9	44.27 ± 2.37*	43.3 ± 2.37*	41.5 ± 1.7
Glucose (mg dL^{-1})	TIVA	51 ± 10.58	55.33 ± 3.21	51 ± 6.92	45 ± 6
	PIVA	41 ± 7.55	46.33 ± 15.5	37.33 ± 7.76	44.67 ± 8.96
Lactate (mmol L^{-1})	TIVA	0.68 ± 0.61	0.3 ± 0	0.3 ± 0	0.38 ± 0.13
	PIVA	0.39 ± 0.10	0.3 ± 0	0.3 ± 0	1.13 ± 1.44
HCO_3- (mmol L^{-1})	TIVA	30.77 ± 3.48	30.3 ± 3.30	30.33 ± 4.13	26.57 ± 2.17
	PIVA	28.57 ± 4.08	31.9 ± 4.38	32.5 ± 3.95	29.37 ± 3.55

* significantly different within the same group compared to baseline. a, b significantly different between groups ($p < 0.05$).

Table 4. FE'Iso (%) (mean ± DS) of isoflurane (PIVA) and micrograms (µg kg^{-1} $minute^{-1}$) (mean ± DS) administered during constant propofol infusion (TIVA), observed in goats undergoing abomasotomy and receiving continuous infusion of fentanyl (10 µg kg^{-1} $hour^{-1}$), lidocaine (50 µg kg^{-1} $minute^{-1}$) and ketamine (50 µg kg^{-1} $minute^{-1}$).

Treatment	**Variable**	**Time points**							
		T0	T1	T2	T3	T4	T5	T6	T7
PIVA	FE'I*so* (%)	0.76± 0.20	0.77± 0.18	0.78± 0.16	0.87± 0.19	0.86± 0.22	0.87± 0.24	0.79± 0.22	0.77± 0.19
TIVA	µg kg-^{1} min-^{1}	421.1± 56.22	447.8± 61.19	458.9± 60.71	447± 57.18	440± 82.76	447.8± 77.42	455.6± 85.89	406.7± 81.7

* significantly different within the same group compared to T0 ($p < 0.05$).

Table 5 Surgery time, anaesthetic time and specific recovery times (mean ± DS and range) observed in goats undergoing abomasotomy and receiving continuous infusion of fentanyl (10 μg kg^{-1} $hour^{-1}$), lidocaine (50 μg kg^{-1} $minute^{-1}$) and ketamine (50 μg kg^{-1} $minute^{-1}$) in conjunction with isoflurane (PIVA) or continuous infusion of propofol (TIVA) for anaesthetic maintenance.

Treatment	Surgery time (minutes)	Anaesthetic time (minutes)	Time to extubation (minutes)	Time to first head lift (minutes)	Time to sternal recumbency (minutes)	Time to standing (minutes)
TIVA	53.1 ± 6.7a (43-63)	100.5 ± 13.3a (70-121)	15.3 ± 4.8a (10-24)	22.7 ± 10.7a (15-47)	27.4 ±11.9a (17-52)	44.3 ± 11.7a (26-69)
PIVA	57.1 ± 9.7a (42-76)	102 ± 15.6a (86-139)	14.7a ± 5.6a (7-27)	18.8 ± 6a (11-28)	22.5 ± 6.8a (14-34)	42.3 ± 14.9a (24-62)

a, b significantly different between groups ($p < 0.05$).

Table 6 Proportion (%) of goats displaying specified behavioural responses during recovery of goats undergoing abomasotomy and receiving continuous infusion of fentanyl (10 μg kg^{-1} $hour^{-1}$), lidocaine (50 μg kg^{-1} $minute^{-1}$) and ketamine (50 μg kg^{-1} $minute^{-1}$) in conjunction with isoflurane (PIVA) or continuous infusion of propofol (TIVA) for anaesthetic maintenance.

Treatment	Behavioural reactions during the recovery	%
PIVA	Ataxia	100
	Chewing movements	33.3
	Exaggerated tail-wagging	33.3
	Nystagmus	22.2
	Vocalizations	11.1
	Restlessness	0
	Kicking	0
	Paddling	0
TIVA	Ataxia	100
	Chewing movements	77.7
	Restlessness	66.6
	Exaggerated tail-wagging	55.5
	Kicking	44.4
	Vocalizations	33.3
	Nystagmus	22.2
	Paddling	22.2

8. CONCLUSIONES GENERALES

En cabras anestesiadas con propofol o isoflurano y la infusión constante de fentanilo-lidocaína-ketamina en las dosis administradas, produjo una adecuada anestesia durante el procedimiento quirúrgico con cambios mínimos en la función cardiopulmonar. Sin embargo, las recuperaciones de la combinación de propofol-fentanilo- lidocaína-ketamina son de mala calidad.