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Subarachnoid ketamine and ketamine s (+) associated with lidocaine in sheep and goats anesthesia

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ABSTRACT

Ten male sheep (Sheep group; SGk) and seven male goats (Goat group; GGks+) were used in this study. The objective was to compare the use of racemic ketamine or ketamine S(+) associated with lidocaine on spinal anesthesia and evaluate if the drugs leads to a surgical anesthesia state, as well as to verify the cardiorespiratory, sedative and motor effects of this technique in these species. After correct placement of the needle in the subarachnoid space, 3.0 mg kg^{-1} of racemic ketamine (SGk) or ketamine S(+) (GGks+), both diluted in 1.5 mg kg^{-1} of 2% lidocaine, were administered. Evaluations were performed during orchiectomy, at times 0 (T0), 5 (T5), 10 (T10), 20 (T20), 30 (T30) and 60 (T60) minutes after subarachnoid anesthesia administration. No significant changes in heart and respiratory rates were observed in both experimental groups. All animals showed surgical analgesia and stood conscious or slightly sedated with ataxia immediately after the drugs administration (T5), allowing the execution of bilateral orchiectomy. The ataxia in SGk was classified as severe with recumbency in 80% of the animals, moderate ataxia in 10% of the animals, and mild ataxia in 10% of the animals. All goats (GGks+; 100%) presented severe ataxia and recumbency. At 60 min, animals of both groups were in standing position and with normal gait. Subarachnoid RS-ketamine and ketamine S(+) (3 mg kg^{-1}), associated with lidocaine in sheep and goats, produces surgical anesthesia and recumbency without causing cardiorespiratory abnormalities, regurgitation and bloating.

1. Introduction

Anesthetic and analgesic techniques are required when painful surgery is going to be performed in small ruminants. Apart from improving animal welfare standards, anesthesia and analgesia are essential to make the procedures easier and improve both animal and personnel safety (Galatos, 2011). Most general anaesthetics induce respiratory and cardiovascular depression and remove normal protective reflexes such as coughing and temperature control. There are some additional problems in ruminants when anesthesia of sheep or goats is performed, distention of the rumen becomes a hazard and regurgitation can follow. Hence, physical restraint and local anesthetic techniques are most commonly used to achieve immobility and analgesia for sheep and goats (Lin, Caldwell & Pugh, 2012).

In small ruminants the subarachnoid anesthesia is used to perform surgical procedures of the tail, perineum, pelvis and hindlimbs, as well as for obstetric maneuvers (Aithal, Amarpal & Singh, 1996; Lumb & Jones, 1984). Traditionally the local anesthetics are the most used for these types of anesthesia (De Rossi, Junqueira, Gaspar & Beretta, 2002). However, the addition of ketamine in subarachnoid anesthesia has shown the advantage of pain management without interfere significantly in cardiovascular and respiratory systems (De Rossi et al., 2002; Strümper et al., 2004). The ketamine is a dissociative anesthetic agent, that can be used clinically in its racemic form or as isomer (ketamine *S*+)

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(Luft & Mendes, 2005; Oliveira, Sakata, Machado & Garcia, 2004; Strümper et al., 2004). This drug is an arylcyclohexylamine derivative from the phencyclidine. It acts upon the N-methyl-D aspartate receptors (NMDA), which is a glutamate subtype receptor widely distributed at all levels of the spinal cord (Lumb & Jones, 1984). The mechanism of action involves synaptic inhibition of these receptors and it is closely related to the treatment of chronic and acute pain Sukiennik and Kream (1995). The ketamine S(+) is considered to be 3 to 4 times more potent than the dextrorotatory enantiomer of ketamine (ketamine R-) for pain relief in humans patients and, in equianalgesic doses, ketamine S(+) produces less central side effects than the racemic and the R(-) enantiomer form (Koinig, Marhofer & Krenn, 2000; Luft & Mendes, 2005; Oliveira et al., 2004).

The subarachnoid ketamine analgesia could be improved by the combined use of lidocaine (Nobrega Neto et al., 2002). This association allows the use of subarachnoid ketamine at subanesthetic doses achieving analgesic efficiency without inducing changes in cardiopulmonary function, which minimizes the stress response induced by surgery and anesthesia (Ozaki et al., 1994).

The availability of a safe anesthetic protocol has great importance when the anesthetist has to deal with painful surgical procedures. The objective of this study was to compare the subarachnoid anesthesia with RS-ketamine racemic and ketamine S(+) associated with lidocaine, and evaluate if both drugs can induce surgical anesthesia in sheep and goats as well as to verify the cardiorespiratory, sedative and motor effects in these species.

2. Materials and methods

This study was approved by the Research Ethics Committee of the Institution under protocol nº 6,925,080,119.

The experimental animals were divided into two trial groups. One group consisting of 10 sheep (SGk), male, adults, mixed breed, body weight 28.9 ± 9.07 kg, that received subarachnoid RS-ketamine and lidocaine. The second group consisted of 7 goats (GGks+), male, adults, mixed breed, body weight 19.2 ± 7.8 kg which received subarachnoid ketamine S(+) and lidocaine. After the anesthetic procedure both groups underwent bilateral orchiectomy. After anesthetic recovery the animals received three doses of 20,000 IU/kg bwt i.m. of benzathine benzylpenicillin (Pentabiótico Reforçado, Zoetis, Brazil) every 48 h, and 1.1 mg/kg bwt i.v. of flunixin meglumine (Banamine, MSD, Brazil) every 24 h for 3 days. The sheep and goat's general condition and surgical site were evaluated twice daily for 5 days, then once daily until wound healing. Drugs used in this study were in accordance with the local laws for food-producing animals.

During the pre-experimental period, the animals were given abamectin as deworming medication and kept in coast-cross paddock with water *ad libitum*. Twenty-four hours before the experimental procedure, the animals were kept in a stable and fasted.

After manual palpation and localization of the space between the last lumbar vertebra and the first sacral, lumbosacral region was clipped and povidone iodine antisepsis was performed. All animals received subcutaneous local anesthesia of 1 ml of lidocaine 2% (Lidocaine 2%, Cristália, Brazil) before spinal injection. The spinal anesthesia was performed with a 18 -gage x 40 mm sterile hypodermic needle. The needle tip was advanced gently until cerebrospinal fluid (CSF) was encountered to confirm access to the subarachnoid space.

After the needle was positioned in the lumbosacral subarachnoid space, sheep (SGk) received RS-ketamine (5% Ketamin, Cristália, Brazil) and goats (GGks+) received ketamine S(+) (5% Ketamin S(+), Cristália, Brazil), both at a dose of 3.0 mg kg^{-1}, diluted in 1.5 mg kg^{-1} of 2% lidocaine (Xylestesin, Cristália, Brazil). The same vials were used for multiple injections only during the same day of anesthetic procedure.

The parameters evaluated for both experimental groups were heart rate (HR), measured using a stethoscope; respiratory rate (RR), measured by observing the movements of the ribs; temperature; presence or absence of ruminal bloating and regurgitation.

The degree of sedation was assessed by the following scale: 1) consciousness: animal was aware of its surrounding and resisted restraint (no sedation), 2) mild sedation: animal attempted to raise its head, move its forelimbs, and had a closed mouth and open eyes, 3) moderate sedation: animal relaxed on the table, moved forelimbs, and had a closed mouth and open eyes, 4) severe sedation: animal relaxed on the table with extended neck and closed mouth and eyes (Daradka & Ismail, 2014). The scrotum skin was tested for analgesia using a 21 -gage x 25 mm sterile hypodermic needle. The results were classified according to the following scale: 1) normal sensation to pain stimulus, 2) mild analgesia, 3) moderate analgesia, 4) complete analgesia which allowed to perform orchiectomy. Hindlimb motor block was evaluated by the following scale: 1) standing animals, 2) mild ataxia, 3) moderate ataxia, 4) severe ataxia and recumbency. Evaluations were performed by blinded observers at times 0 (T0), just before subarachnoid anesthesia, and at 5 (T5), 10 (T10), 20 (T20), 30 (T30) and 60 (T60) minutes after subarachnoid anesthesia administration.

Data were analyzed with Sigma Stat for Windows version 2.0 (Jandel Corporation, San Rafael, CA, USA). The normality of the distribution was evaluated by the Kolmogorov–Smirnov test. A one-way ANOVA with repeated measures, followed by a Student–Newman–Keuls test, was performed for numerical data and categorical data were analyzed with the Fisher's exact test. Differences were considered significant when $p \leq 0.05$.

3. Results and discussion

No significant differences or abnormalities in temperature, heart and respiratory rates were observed among times inside each experimental group or between groups (Table 1). This is in accordance with previous results (Daradka & Ismail, 2014; De Rossi, Junqueira, Lopes & Beretta, 2005). None of the animals presented regurgitation or ruminal bloating. Follow-up on the operated sheep and goats showed that all wounds were fully healed without any significant complications.

Subarachnoid anesthesia with 5% RS-ketamine or 5% ketamine S(+), both at a dose of 3.0 mg kg^{-1}, diluted in 1.5 mg kg^{-1} of 2% lidocaine, provided mild sedation in sheep and goats and produced anesthesia of the inguinal area. Considering degrees of sedation, analgesia and hindlimb motor block there were no significant differences between groups, but time differences inside each group were observed.

Regarding sedation, the animals of both experimental groups showed signs of consciousness or mild sleepiness (scoring 1 or 2), from T5 to T30, being conscious at T60 (scoring 1 for 100% of the SGk and GGks+ animals) (Table 1). Both anesthetic protocols, performed in SGk and GGks+, provided surgical analgesia for bilateral orchiectomy, and all animals (100%) scored 4 for the analgesia parameter, starting at T5, lasting until T30 (Table 1). The analgesic and anesthetic effects observed 5 min after the drugs administration was satisfactory, since the surgical manipulation did not provide cardiorespiratory changes, movements or vocalization in both experimental groups. Ketamine, even at subanesthetic doses, retains analgesic properties (Corssen and Domino, 1996; Ryder, Way & Trevor, 1978), and when associated with lidocaine promotes anesthesia and surgical analgesia, which is in agreement with this study findings.

Errando, Sifre and Moliner (2004) demonstrated that the anesthetic and analgesic effect of ketamine is related to the antagonist action on N-methyl-D-aspartate receptors (NMDA), which have implications for pain perception and chronic pain development. Local anesthetics, such as lidocaine, are agents that, when applied in adequate concentration, reversibly block nerve conduction of sensory and motor impulses (Carvalho & Luna, 2007; Massone, 2003). Due to the rapid onset of analgesia, absence of sedation, and the small volume of drugs used, it is suggested that the anesthetic action is mediated by direct spinal action of the administered drugs and not by systemic absorption and central nervous system effect (Di Filippo, Ribeiro, Dória, Costa & Valadão, 2004)

Table 1
Mean values and standard deviation of heart (HR) and respiratory (RR) rates, degree of sedation, analgesia and hindlimb motor block (percentage;%), observed in the Sheep Group (SGk; $n = 10$) and in the Goat Group (GGks+; $n = 7$) over the time.

Parameter	Group	0	5	10	20	30	60
HR	**SGk and GGks+**	118 ± 12	135 ± 14	128 ± 11	92 ± 8	128 ± 8	110 ± 12
RR		33 ± 3	25 ± 1	30 ± 3	35 ± 4	37 ± 6	30 ± 3
	SGk	100%: 1[a]	80%: 2[b]	80%: 2[b]	80%: 2b[b]	80%: 2[b]	100%: 1[a]
Sedation			20%: 1	20%: 1	20%: 1	20%: 1	
	GGks+	100%: 1[a]	86%: 2[b]	100%: 2[b]	100%: 2[b]	100%: 2[b]	100%: 1[a]
			14%: 1				
Analgesia	**SGk**	100%: 1[a]	100%: 4[b]	100%: 4[b]	100%: 4[b]	100%: 4[b]	100%: 2[c]
	GGks+	100%: 1[a]	100%: 4[b]	100%: 4[b]	100%: 4[b]	100%: 4[b]	100%: 2[c]
	SGk	100%: 1[a]	80%: 4[b]	80%: 4[b]	80%: 4[b]	80%: 4[b]	100%: 1 [a]
Hindlimb motor block			10%: 3	10%: 3	10%: 3	10%: 3	
			10%: 2	10%: 2	10%: 2	10%: 2	
	GGks+	100%: 1	86%: 4[b]	100%: 4[b]	100%: 4[b]	100%: 4[b]	100%: 1[a]
			14%: 3				

Different letter (a, b and c) represents a statistically difference among time inside the group; $p \leq 0{,}05$. **Sedation:** 1) consciousness: animal was aware of its surrounding and resisted restraint (no sedation), 2) mild sedation: animal attempted to raise its head, move its forelimbs, and had a closed mouth and open eyes, 3) moderate sedation: animal relaxed on the table, moved forelimbs, and had a closed mouth and open eyes, 4) severe sedation: animal relaxed on the table with extended neck and closed mouth and eyes; **Analgesia:** 1) normal sensation to pain stimulus 2) mild analgesia 3) moderate analgesia 4) complete analgesia which allowed to perform orchiectomy; **Hindlimb motor block:** 1) standing animals 2) mild ataxia 3) moderate ataxia 4) severe ataxia and recumbency.

Additionally, in this study consciousness was maintained and only mild sedation was achieved following subarachnoid administration of lidocaine-associated RS-ketamine or ketamine S(+) in sheep and goats. The same effect was also reported in studies conducted by De Rossi et al. (2002). It can be assumed that a slow systemic absorption of ketamine from the subarachnoid space is responsible for the mild sedative effects, while providing local analgesic effects and ataxia. It is considered that the liver of goats may be quicker in detoxifying or metabolizing drugs (Lin et al., 2012). However, the effect of ketamine S (+) administered in the same dose of racemic ketamine did not allow this assumption, since the sedative effect was similar in both experimental groups.

Regarding hindlimb motor blockade, it was observed in SGk severe ataxia and recumbency in 8 animals (80%), moderate ataxia and ambulation in 1 animal (10%) and mild ataxia in 1 animal (10%). These changes were observed immediately after the subarachnoid administration of the drugs (T5) and lasted for 30 min (T30). Animals that showed moderate and mild ataxia, respectively, remained in dorsal recumbency without additional sedation for 30 min. At 60 min (T60) all animals were in quadrupedal position and presented normal gait. In the GGks+ animals, 6 animals (86%) scored 4 in T5, which corresponds to severe ataxia and recumbency and 1 animal (14%) scored 3 in the first evaluation (T5), which corresponds to moderate ataxia, and later (T10) scored 4. All animals remained in recumbency until T30, at 60 min they were in quadrupedal position and with normal gait (Table 1).

These results are in contrast with the literature that have reported moderate ataxia in goats following subarachnoid administration of ketamine (De Rossi et al., 2002). Lidocaine can completely block nerve conduction and also depress pre and postjunctional impulse conduction (Braga et al., 2009; Steinbach, 1968). It is hypothesized that subarachnoid lidocaine is responsible for the motor blockade of the hindlimbs, and may cause recumbency in animals by local blockade of sympathetic sensory and motor innervations.

Similarly, it is assumed that the difference found between the SGk and GGks+ groups in the degree of sedation and hindlimb motor block, promoting recumbency (80% SGk and 100% GGks+) is due to the use of racemic ketamine in SGk and ketamine S(+) in GGks+ at the same dose (3 mg kg^{-1}). It is known that ketamine S(+) is considered up to 2.5 times more potent than the racemic ketamine (Luft & Mendes, 2005), and probably contributed for the greater number of animals that presented higher degree of sedation, ataxia and recumbency in the GGks+ animals. On the other hand, the 1.5 mg kg^{-1} dose of ketamine S(+) associated with spinal lidocaine in goats did not promote surgical analgesia in 20% of the animals (Di Filippo et al., 2004). This suggests the need to use a higher dose of this drug, as it was used in this study.

Subarachnoid anesthesia protocol used in this study promoted surgical analgesia, allowing 100% of bilateral recumbent orchiectomies with only mild sedation of the animals, without changing cardiorespiratory parameters, promoting regurgitation or bloating. Daradka and Ismail (2014) showed that RS-ketamine at 1.5 mg/kg and lidocaine at 1.25 mg/kg administered intrathecally at the lumbosacral intervertebral space provided safe and effective analgesia of the caudal abdominal and udder region sufficient to perform mastectomy or hemimastectomy in goats. However, the animals delayed 15 min to reach the maximal analgesia and presented significant rise in heart rate at some point between 5 and 90 min. In the present study, we evaluated a higher dose of subarachnoid ketamine and lidocaine and we observed faster maximal analgesic effect (T5), similar hindlimb motor block and recumbency without present vital signs abnormalities or neurotoxic symptoms during the anesthetic and post-anesthetic period.

Combined with the fact that the anesthetic protocols presented in this study provide surgical analgesia in 100% of the animals (10 sheep and 7 goats), it is worth mentioning the comfort and safety of subarachnoid anesthesia in sheep and goats for surgeries that takes up to 30 min. Eighty percent (SGk) and 100% (GGks+) of the animals remained in dorsal recumbency due to motor blockade of the hindlimbs, although conscious or slightly sedated, recovering the quadrupedal position after 60 min of drug administration. During this period, none of the animals presented reactions commonly observed after intravenous infusion of ketamine and ketamine S(+) in the anesthesia of small ruminants that could indicate side effects of subarachnoid drug administration like cardiorespiratory depression, regurgitation or ruminal bloating (Hall & Clarke, 1983; Natalini, Mollerke & MOTTA, 1993; Strümper et al., 2004).

Some limitations should be noted in the present study. First, the study enrolled sheep and goats only in the RS-ketamine and ketamine S (+) group, respectively. Second, the number of animals was not homogeneous between groups and an effect associated with the breed could have influenced the results. Third, the assessment of the degree of analgesia was subjective and fourth, the study lacks of a positive control group evaluating subarachnoid lidocaine only and results should be interpreted cautiously regarding the analgesic properties of RS-ketamine and ketamine S(+).

4. Conclusion

The results of this study suggest that subarachnoid RS-ketamine and ketamine S(+) associated with lidocaine in sheep and goats produce surgical analgesia and recumbency without causing cardiorespiratory

abnormalities, regurgitation or ruminal bloating.

Ethical animal research

This study was approved by the Research Ethics Committee of the Institution under protocol nº 6,925,080,119.

Declaration of Competing Interest

The authors declare that there is no financial/personal conflict of interest.

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