ABSTRACT
The objective of the study was to determine the analgesic and systemic effects of subarachnoid administration of xylazine hydrochloride (XY), lidocaine hydrochloride (LI) and their combination (XYLI) in goats. Six healthy goats were used in a prospective randomised study. Three treatments were administered to each goat, with 1-week intervals between each treatment. Treatments consisted of 0.1 mg/kg xylazine, 2.5 mg/kg lidocaine and a combination of xylazine 0.05 (mg/kg) and lidocaine (1.25 mg/kg). Analgesia, ataxia, sedative, cardiovascular and respiratory effects, and rectal temperature were evaluated before (baseline) and at 5, 10, 15, and 30 min after subarachnoid injection, and then at 30-min intervals until loss of analgesia occurred. Lidocaine induced analgesia in 3.1 ± 1 min (mean ± SD), which lasted for 66 ± 31 min. Heart and respiratory rates and blood pressure remained unchanged after lidocaine-induced analgesia. Xylazine induced analgesia in 9.5 ± 2.6 min and xylazine-lidocaine in 3.2 ± 1.2 min. Xylazine-lidocaine-induced analgesia lasted longer (178 ± 37 min) than that induced by xylazine (88.3 ± 15 min). The XYLI treatment induced prolonged motor blocking (115 min), more than the XY (80 min) and LI (90 min) treatments. Both xylazine and xylazine-lidocaine caused significant decreases in the heart and respiratory rates, but not in blood pressure. The combination of xylazine (0.05 mg/kg) and lidocaine (1.25 mg/kg) can be administered subarachnoidally (between last lumbar vertebra and 1st sacral vertebra) to produce prolonged (>2.5 h) analgesia of the tail, perineum, hind limbs, flanks and caudodorsal rib areas in goats. Despite the prolonged analgesia, using this combination is desirable for relieving postoperative pain, but it may be a disadvantage due to a motor block when dealing with goats.

Key words: analgesia, goats, lidocaine, subarachnoid, xylazine.

INTRODUCTION
Epidural or subarachnoid anaesthesia is considered to be advantageous for general anaesthesia in ruminants25. Local anaesthetics have the potential to produce sensory, motor and sympathetic blocking by depressing aonal conduction of nerves. Onset of local anaesthetic effects is characterised by severe motor blocking in the hind limbs. Usually 2 % lidocaine is used with this objective, but higher doses and concentrations induce lesions of the nervous tissues in a temporary or irreversible way26,27. The vasodilatation due to sympathetic blocking produced by subarachnoidally-injected local anaesthetics decreases the duration of anaesthesia25,34 and induces hypotension30.

The use of alpha-2 adrenergic agonists has become popular for epidural or subarachnoid analgesia in goats28, horses22,24 and cattle29. Subarachnoidally administered xylazine, an alpha-adrenergic agonist most frequently used in veterinary medicine, inhibits spinal substance P release31, and nociceptive neuron firing32 produced by noxious stimuli and produces analgesia. However, sedation, hypotension, bradycardia, and respiratory depression may occur in goats7,15,26.

Previous studies demonstrated that lidocaine or xylazine in combination with other drugs after epidural or subarachnoid administration1,16 increased the duration of the analgesic/anaesthetic period. Furthermore, it reduced the doses needed of each drug. All local anaesthetics have a biphasic effect on vascular smooth muscle and at low concentrations tend to cause vasoconstriction11. Large doses of epidural xylazine can trigger severe ataxia and deep sedation in horses22 and goats15. Several studies have shown that local anaesthetics combined with alpha-2 agonist or opioid drugs produce an increase in pain relief duration with epidural administration in humans28,32,33. The purpose of the present study was therefore to determine whether the combination of low doses of lidocaine and xylazine administered by the subarachnoid route in goats produces analgesia of longer duration with fewer side-effects than subarachnoid lidocaine or xylazine administered alone at doses clinically used in veterinary medicine.

MATERIALS AND METHODS
Six adult healthy goats (1 male and 5 females) ranging from 12 to 26 months in age and from 23 to 40 kg (mean, 30 kg) were selected for the study. The experimental animals were kept at the Veterinary Science Centre, Federal University of Mato Grosso do Sul State, under uniform management conditions and also accustomed to the personnel conducting the experiments. Goats were allowed ad libitum access to food and water until the beginning of each experiment and were also allowed to eat hay during the experiment. The observers were blinded to the drugs and doses administered in each study. Each animal received xylazine hydrochloride (Dorcipex 2 %, Vallée Veterinary Products Ltda, São Paulo, Brazil) (0.1 mg/kg), 2 % lidocaine hydrochloride (Lidocaína sem vasoconstritor 2 %, Hipo-labor Farmacêutica Inc, Sabará, Brazil) (2.5 mg/kg) or xylazine (0.05 mg/kg) and 2 % lidocaine (1.25 mg/kg), in random order at 1-week intervals. The study was approved by the Ethics Committee of Federal University of Mato Grosso do Sul State.

All animals received 3 treatments. The area was aseptically prepared, clipped, and scrubbed with povidone-iodine and infiltrated with lidocaine 1 % (1 ml) at the entry point. The hypodermic needle (20-gauge, 3.5 cm long) was directed to the spinal cord at a 45° angle along the median plane. The lumbosacral space was identified by the depression between the

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Received: November 2004. Accepted: May 2005.


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last lumbar vertebra and the 1st sacral vertebra and the presence of the needle in the subarachnoid space was confirmed by a free flow of CSF from the needle. Three treatments used were: xylazine, 0.1 mg/kg (XY; mean dose 3.5 mg); 2% lidocaine, 2.5 mg/kg (LI; mean dose 95 mg), and xylazine, 0.05 mg/kg and 2% lidocaine, 1.25 mg/kg (XYLI; mean dose 1.75 mg and 45 mg). The volume of all treatments was adjusted to 1 m/7.5 kg body weight by the use of saline (0.9%) solution (Hidrate®, Pharmaceutical Products Ltda, Campo Grande, Brazil), when necessary. The drugs were injected in the subarachnoid space of each experimental animal.

Heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO2), and arterial blood pressure [systolic (SAP), mean (MAP), and diastolic (DAP)] were recorded before injection (baseline), 5, 10 and 15 min after injection, and at 30-min intervals thereafter until the analgesic effect disappeared. Arterial blood pressures were measured using a non-invasive device (EMAI-RX 300 blood pressure monitor, Transmai Equipamentos Médicos Hospitalares Ltda, São Paulo, Brazil), with the cuff attached to the proximal third of the radius in order to measure the pressure in the brachial artery. The peripheral oxygen saturation (SpO2) was measured through a sensor (EMAI-RX 300 oxygen monitor, Transmai Equipamentos Médicos Hospitalares Ltda, São Paulo, Brazil) attached to the inguinal pleat, which had been shaved. The heart rate (HR) was measured through an electrocardiograph (EMAI-RX 300 cardiac monitor, Transmai Equipamentos Médicos Hospitalares Ltda, São Paulo, Brazil). Arterial pressure, heart rate and SpO2 were measured using a cardiac monitor (RX-300®, São Paulo, Brazil). The respiratory rate (RR) was measured by counting the chest movements per minute, and the rectal temperature (RT) was measured with a digital thermometer (°C) (Digital Thermometer, Becton Dickinson Inc., Ottawa, Canada.)

All cardiovascular and respiratory variables were recorded before noxious stimulation to establish non-stimulated values. Effects like salivation and urination frequency were also monitored.

Onset and duration of analgesia was determined with a 22-gauge, 2.5-cm-long needle to assess superficial (needle used to prick the skin) and deep (needle inserted into the muscles) pain in the tail, perineum, hind limbs, flanks and caudodorsal rib areas. Response to these stimuli was rated according to the following scale: 1, no analgesia (normal strong reaction to painful stimulus); 2, mild analgesia (depressed reaction to painful stimulus); 3, moderate analgesia (no response to needle-prick stimulation of the skin); and 4, complete analgesia (no response to insertion of the needle deep into the muscle). The degree of sedation was evaluated at each of the recording times after the treatments were given. Grading was performed as follows: 1, no sedation effect; 2, mild sedation (reduced alertness without other signs of sedation); 3, moderate sedation (drowsiness and slight drooping of the head); and 4, severe sedation (severe drowsiness). Ataxic effects were evaluated using the following scale: 1, no ataxia; 2, mild ataxia (difficulty in maintaining a standing position); 3, moderate ataxia (recumbent with movement of hind limbs); and 4, severe ataxia (recumbent without movement of hind limbs). All clinical variables were evaluated immediately before subarachnoid injection (baseline) and at 5, 10, 15, 30 min following drug administration and thereafter at 30-min intervals. To assess the diffusion extent of all solutions within the subarachnoid space at different intervals, superficial skin pricks and deep needle pricks into the muscle were made at adjacent dermatome regions, beginning at the tail and proceeding cranially up to the caudodorsal rib area.

Data were analysed using the Statistical Analysis System (SAS 6.12, SAS Institute Inc., Cary, NC, USA). A randomised block design was used for each drug, with time as treatment and each of the 6 animals as a block. For dependent variables HR, SAP, DAP, MAP, RR, SpO2, and RT analysis of variance differed from baseline (time 0). For analgesia, ataxia and sedation-dependent variables, the non-parametric Friedman test was used, followed by multiple data comparisons. The Dunnett rank test was also applied, with time 0 being considered as baseline. In each analysis, differences were considered significant if P < 0.05.

RESULTS

Subarachnoid injection of the drugs at the lumbosacral space was made without any problems in all animals. The analgesia test through a needle-prick was efficient and demonstrated which dermatomes were blocked after subarachnoid administration of the drugs. The onset of analgesia began in the tail and after that spread to other regions, progressing cranially to the flanks. The xylazine-lidocaine combination produced a longer duration of complete analgesia (178.3 ± 37 min, mean ± SD) than xylazine (88.3 ± 15 min) or lidocaine (66 ± 31 min) alone in the region of the tail, perineum, hind limbs, flanks and dorsocaudal rib areas in goats. Complete analgesia (grade 4) began in 3.2 ± 1.2 min in the XYLI treatment, similar to the LI treatment (3.1 ± 1 min), but the onset was delayed with the XY treatment (9.5 ± 2.6 min) (Fig. 1). The extent of analgesia obtained with the XYLI treatment was similar to that obtained with the XY treatment, extending to dermatome region L13 to L12, but with the LI treatment, analgesia extended only up to dermatome region L14. All animals in the 3 groups showed ataxia and subsequently attained sternal recumbency. The ataxic effect was more prolonged in the XYLI treatment, lasting 115 min (score 4), while in the XY and LI treatments, it lasted 80 min and 90 min, respectively (Fig. 2). Subarachnoid administration of the XY or XYLI treatments induced sedation; however, it was more evident and prolonged after the XY treatment (Fig. 3). Salivation was evident in all goats at all intervals after the XY treatment, and from 10 to 30 min in the

Fig. 1: Median antinociception score in response to a standard noxious stimulus in the tail, perineum, hind limbs, flanks and caudodorsal rib areas after subarachnoid administration of xylazine (XY; 0.1 mg/kg), lidocaine (LI; 2.5 mg/kg) or xylazine/lidocaine (XYLI; 0.05 mg/kg and 1.25 mg/kg, respectively) in 6 goats. The following scale was used: 1, no analgesia; 2, mild analgesia; 3, moderate analgesia; and 4, complete analgesia. a,b,cThe value for 4XYLI, 3LI, and 2XY differed significantly (P < 0.05) from the respective baseline (time 0) value.
Xyli treatment. Also, all goats urinated frequently (mean of 3 times) throughout the experimental period after subarachnoid administration of the XY or XYLI treatments.

Subarachnoid injection of xylazine induced a significant decrease \( (P < 0.05) \) in HR, compared with the baseline value, from 10 min after injection until the end of the experiment. The XYLI treatment caused significant decreases \( (P < 0.05) \) in HR from 30 to 90 min. The LI treatment did not cause significant differences \( (P < 0.05) \) in HR at any time interval. Arterial pressures (SAP, DAP and MAP) did not change significantly from baseline values following the subarachnoid XY, LI or XYLI treatments (Table 1). Respiratory rate decreased significantly from 10 to 150 min after the XY treatment and there was also a significant decrease in \( \text{SpO}_2 \), from 10 to 30 min after the XY treatment. The XYL treatment decreased RR significantly \( (P < 0.05) \) at 15 min, but did not alter peripheral \( \text{O}_2 \) significantly. Four goats given the XY treatment and 1 goat given the XYLI treatment had irregular and reduced RR 10 min after injection, but all of them returned to baseline values at the end of the experiment. Rectal temperature remained stable after the XYLI treatments, but the subarachnoid XY or LI treatments induced a significant decrease \( (P < 0.05) \) in RT, compared to the baseline value, from 60 to 150 min and from 5 to 180 min, respectively (Table 2).

**DISCUSSION**

The results of the study indicated that the subarachnoid administration of xylazine-lidocaine induced analgesia in the regions of the tail, perineum, hind limbs, flank and caudodorsal ribs in goats, and regions of the tail, perineum, hind limbs, flank and caudodorsal ribs in goats, and regions of the tail, perineum, hind limbs, flank and caudodorsal ribs in goats. Adverse effects of subarachnoidly-administered xylazine included sedation, decrease in HR and RR, ataxia, recumbency and increase in salivation and frequency of urination. In our experiment, xylazine-lidocaine at a dosage of 0.05 mg/kg and 1.25 mg/kg, respectively, administered subarachnoidly produced analgesia with a duration twice as long \( (178.3 \pm 37 \text{ min}) \) as that observed after administration of xylazine \( (88.3 \pm 15 \text{ min}) \) or lidocaine \( (66 \pm 31 \text{ min}) \) alone. The onset of the analgesia of the studied regions, which firstly began in the tail and extended to cranial dermatomes was \( \geq 3 \text{ min} \) in the XYL and LI treatments, but the onset in the XY treatment was more delayed \( (9.5 \pm 2.6 \text{ min}) \). Analgesia produced by epidural or subarachnoid administration of lidocaine has a faster onset compared to xylazine in goats\(^4\) and medetomidine in cows\(^6\). Similar results were obtained in the present study with local anaesthetics such as xylazine producing a delayed response to the onset of analgesia. A delayed onset of analgesia by xylazine compared to lidocaine has been reported in various animals\(^7,12,16\). The duration of analgesia in the studied regions after subarachnoid administration of half-doses of lidocaine in combination with the half-doses of xylazine caused analgesia blocking with a 2-fold longer duration than that observed with the use of either drug alone at full dose. Compared to local anaesthetics, but similar to opioids, detailed studies have shown that alpha-2 agonists tend to produce variable or patchy segmental effects\(^8,14\). For this reason, xylazine and the opioids are often combined with other drugs, such as local anaesthetics, for caudal epidural analgesia in horses\(^15,37\). The effect of subarachnoidly-applied local anaesthetic drugs on spinal blood flow is of interest because disturbances in normal neurological function and neurotoxicity can result from reduced blood flow\(^11,14,38\). Alpha-2 adrenergic stimulation of vascular smooth muscle by xylazine via activation of post-synaptic alpha-2 adrenoceptors may reduce spinal blood flow, producing spinal ischaemia with neuronal damage. However, in slow doses the spinal blood flow was not influenced by the epidural administration of a preservative-free alpha-2 agonist solution in sheep\(^11\) or horses\(^5\).

Agonists of alpha-2 adrenergic receptors produce analgesia by their action on receptors in the substantia gelatinosa of the dorsal horn of the spinal cord. Xylazine may also have a local anaesthetic-like action on spinal nerves\(^11,33\). All animals given the 3 treatments – XY, LI or XYLI – presented incoordination and recumbency, being more delayed in the XYLI treatment, which suggests that xylazine may also have had a local anaesthetic action. It has been speculated that some of the efficacy of alpha-2 adrenergic agonists in producing analgesia following their regional injection may result from their local anaesthetic action on A and C fibres\(^1\). Inhibition of the A fibres probably leads to motor blocking. In this study, in the combination treatment, the motor blocking achieved was...
Table 1: Cardiovascular values in 6 goats subarachnoidally administered with xylazine, lidocaine, or xylazine-lidocaine (mean ± SD).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td></td>
<td>XY</td>
</tr>
<tr>
<td>HR</td>
<td>107 ± 14</td>
</tr>
<tr>
<td>DAP</td>
<td>88 ± 22</td>
</tr>
<tr>
<td>SAP</td>
<td>126 ± 6</td>
</tr>
<tr>
<td>MAP</td>
<td>102 ± 7</td>
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</tbody>
</table>

Table 2: Respiratory rate, oxygen saturation and rectal temperature values in 6 goats subarachnoidally administered with xylazine, lidocaine, or xylazine-lidocaine (mean ± SD).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Treatments</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td></td>
<td>XY</td>
</tr>
<tr>
<td>RR</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>$\text{SpO}_2$</td>
<td>99 ± 0.5</td>
</tr>
<tr>
<td>RT</td>
<td>39.5 ± 0.3</td>
</tr>
</tbody>
</table>

*Denotes statistical significance from baseline (P < 0.05).

Systemic effects of subarachnoidally administered xylazine and xylazine-lidocaine were evidenced by profound sedation and salivation, similar to those reported after subarachnoid xylazine administration in goats or cattle, indicating rapid vascular or/and lymphatic absorption from the subarachnoid space. All experimental animals showed an increase in the frequency of urination after subarachnoid administration of xylazine and xylazine-lidocaine. This effect may be associated with the inhibition of antidiuretic hormone release from the pituitary, antagonism of the renal tubular action of antidiuretic hormone, increase in glomerular filtration rate and release of atrial natriuretic factor.

The reduction in rectal temperature observed in goats after administration of xylazine may have been caused by sedation, reduced metabolism, muscle relaxation and depression of the CNS. In addition, alpha-2 agonists reportedly induce prolonged depression of thermoregulation. A combination of these mechanisms could potentially result in hypothermia. A decrease in rectal temperature after administration of anaesthetics has been reported in other studies on goats. In our study, lidocaine induced a long-lasting decrease in rectal temperature, possibly because of regional vasodilatation induced by the anaesthetics.

Cardiovascular effects induced by xylazine are the result of stimulation of peripheral or central alpha-2 adrenoceptors. Stimulation of pre-
junctival alpha-2 adrenoceptors results in inhibition of release of norepinephrine from peripheral nerve endings, which, in part, contributes to the bradycardiac effect of the drugs. Subarachnoid administration of xylazine and xylazine-lido-
caine induced a significant decrease in HR. Heart rate did not show any change after subarachnoid administration of lidocaine. This is similar to the results obtained with epidural xylazine in cattle and mares, epidural clonidine in sheep and subarachnoid xylazine and medetomo-
dine in goats. The decrease in HR was less pronounced in the combination treat-
ment. This might be due to the low dose of xylazine used in this group (0.05 mg/kg). Several mechanisms contribute to the alpha-2 adrenergic agonist-induced bradycardia, which include decreased sympathetic outflow from the central nervous system, inhibition of norepi-
 nephrine release from sympathetic nerve terminals, direct depression of cardiac pacemaker and conduction tissue, in-
creased vagal tone and a direct increase in the release of acetylcholine from parasympathetic nerves in the heart. In this study, arterial blood pressure in the goats that received xylazine and xylazine-lido-
caine did not change significantly from baseline values. In dogs, MAP had a biphasic (increased then decreased) response, similar to that observed after IV administration of medetomidine, and other alpha-2 adrenergic agonist drug, to rats. This biphasic effect is caused by stimulation of the peripheral alpha-2 adrenergic receptors located in the vascu-
lar wall, which is followed by central and peripheral effects resulting in secondary hypotension. Alpha-2 adrenergic ago-
nist drugs have a prevalent peripheral action compared with their central action, this effect being determined by the dose and frequency of administration. Inter-
mediate dose of epidural xylazine, in con-
trast to small or large ones, causes the largest decrease in blood pressure. The fact that higher doses did not result in a more marked decrease in arterial blood pressure was thought to be a reflection of the peripheral alpha-2 receptor effects. Local anaesthetics, like lidocaine cause an indiscriminate blockade of the sensory, sympathetic and motor fibres. The sym-
pathetic block induces vasodilatation in the anaesthetised areas, producing hypotension in clinical doses. In our study, the doses of lidocaine, xylazine and half-doses used in combination did not produce significant decreases in the arte-
rial pressure compared to the basal value. Subarachnoid administration of XY and XYL caused irregularity and a significant reduction in RR, but only the XY treatment decreased SpO2. Significantly decreased respiratory rate and PaO2 were recorded after xylazine administered epidurally in cattle or subarachnoidally in goats and those authors cited literature supporting the idea that the respiratory effects of epidural or subarachnoid administration of xylazine are mediated through alpha-2 adrenoceptors activity.

CONCLUSIONS

The results of this study indicate that injection of a combination of xylazine and lido-
caine in half-doses (0.05 mg/kg and 1.25 mg/kg, respectively) into the sub-
arachnoid space induces more prolonged (>2.5 hours) analgesia in the tail, peri-
neum, hind limbs, flanks and caudo-
dorsal rib areas than that observed with the use of either drug alone at the full dose in goats. However, in combination they caused a significant decrease in heart rate and respiratory rate as well as signifi-
cant ataxia and sedation.

ACKNOWLEDGEMENTS

This study was supported by the Foun-
dation of Teaching, Science and Technol-
ey Development, Mato Grosso do Sul State.

REFERENCES

2. Aithal H P, Amarpal Pratap K, Singh G R 1996 Clinical effects of epidurally adminis-
terated xylazine and ketamine in goats. Small Ruminant Research 24: 55–64.
9. Eisenach J C, Detweller D, Hood D 1993 Hemodynamic and analgesic actions of epidurally administered clonidine. Anesthesi-
siology 78: 277–287
statin and interaction with thyrotropin re-
leasing hormone. Neuroscience 27: 267–278
16. Grubb T L, Reibold T W, Huber M J 1993 Evaluation of lidocaine, xylazine and a combi-
nation of lidocaine and xylazine for epidural analgesia in llamas. Journal of the American Veterinary Medical Association 203: 1441–1444
19. Johns R A, Seyede W C, DiFazio C A, Long-
necke D F 1986 Dose-dependent effects of bupivacaine on rat mesencephalic arteries. Anes-
thesiology 65: 186–191
25. Lumb W J, Jones E W 1984. Spinal anesthe-
sia. In Veterinary anaesthesia (2nd edn), Lea & Febiger, Philadelphia: 408–413


32. Purdie N L, McGrady E M 2004 Comparison of patient-controlled epidural bolus administration of ropivacaine and 0.1 % levobupivacaine, both with 0.0002 % fentanyl from analgesia during labour. Anaesthesia 59: 133–137


