Analgesic and cardiopulmonary effects of intrathecally administered romifidine or romifidine and ketamine in goats (*Capra hircus*)

H P Aithal[a], Amarpal[a], P Kinjavdekar[a], A M Pawde[a] and K Pratap[a]

ABSTRACT

The study was conducted to evaluate the effects of romifidine alone (50 µg/kg) and a combination of romifidine (50 µg/kg) and ketamine (2.5 mg/kg) after intrathecal administration in goats. Ten adult goats of either sex weighing between 15 and 20 kg were randomly placed in 2 groups (groups I and II). The agents were administered at the lumbosacral subarachnoid space. Clinico-physiological parameters such as analgesia, motor incoordination, sedation, salivation, heart rate, respiratory rate, arterial pressure, central venous pressure and rectal temperature were studied. Other haematobiochemical parameters monitored were packed cell volume, haemoglobin, plasma proteins, glucose, urea and creatinine. The onset of analgesia was faster in group II (35.5 ± 6.25 s) compared to that of group I (5.2 ± 0.54 min). Analgesia of the tail, perineum, hind limbs, flank and thorax was mild to moderate in group I, but complete analgesia of tail, perineum and hind limbs was recorded in group II. Motor incoordination was mild in group I and severe in group II. Significant reduction in heart rate (more pronounced in group I) and respiratory rate (more pronounced in group II), and a significant increase in central venous pressure were recorded in both groups. Mean arterial pressure was reduced in both groups, but more markedly in group I. Sedation, electrocardiogram, rectal temperature and haemato-biochemical parameters did not show significant differences between the 2 groups. The results of this study indicated a possible synergistic analgesic interaction between intrathecally administered romifidine and ketamine, without causing any marked systemic effects in goats.

Key words: analgesia, goats, intrathecal, ketamine, romifidine.

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INTRODUCTION

Alpha-2-adrenergic agonists such as xylazine, detomidine and medetomidine have been widely used epidurally and intrathecally (subarachnoid) to bring about more prolonged hindquarter analgesia than the conventionally used lignocaine hydrochloride in ruminants[22,41]. A major disadvantage of the use of α-2 agonists is dose-dependent cardiovascular depression[12]. To overcome this limitation, alpha-2 agonists have been used in combination with other drugs such as local anaesthetics or opioids[8,13,14,18], to reduce the dose and limit the side-effects. Ketamine, a phencyclidine derivative, is a cardiovascular stimulant, which has also been shown to produce a variable degree of hind quarter analgesia, both in man and in animals by acting on N-methyl-D-aspartate (NMDA) receptors after spinal administration[2,9,20]. In previous studies when xylazine and medetomidine were used epidurally or intrathecally together with ketamine, hindquarter analgesia was prolonged and the cardiovascular depressant effect reduced considerably, suggesting synergistic interaction between the NMDA receptor antagonist and the alpha-2 adrenergic agonist[1,3,22,23].

Romifidine, 2-[(2-bromo-6-fluoroplenyl) imino] imidazolidine monohydrochloride, is a specific and relatively new alpha-2 adrenergic agonist drug that is mostly administered systemically to bring about sedation and analgesia[16,21]. To our knowledge, romifidine has not been evaluated for intrathecal use in any animal species. The purpose of this study was to evaluate the analgesic interaction as well as physiological, haematobiochemical and haemodynamic changes produced by romifidine alone and in combination with ketamine after intrathecal administration in goats.

MATERIALS AND METHODS

Ten adult indigenous goats of both sexes in good health, weighing between 15 and 20 kg, aged 12–15 months, were used. All the animals were allowed to stabilise for 10 days, during the period they were fed a standard ration, given water *ad libitum* and were accustomed to being approached. All the animals were starved for 24 hours before the start of the experiments.

Experimental goats were randomly divided into 2 groups, I and II, consisting of 5 animals each. The experiment was conducted in 2 phases. During the first phase, clinico-physiological parameters and blood biochemical changes were studied. In the second phase, haemodynamic changes were evaluated. Ten days were allowed between the 2 phases of the experiment.

One hour before the start of the first phase of the experiment, the animals were taken to a quiet experimental room and allowed to stabilise. The animals of group I were administered intrathecal (subarachnoid) romifidine at a dose of 50 µg/kg body weight (dose volume was adjusted to 2 mℓ using normal saline). In group II, 2 mℓ of a combination of romifidine (50 µg/kg) and ketamine (2.5 mg/kg) was administered simultaneously using different syringes. The doses of drugs was selected based on our earlier studies. In both the groups, the drug/s were injected into the lumbosacral subarachnoid space (presence of needle in subarachnoid space was confirmed by the outflow of cerebrospinal fluid), using a 20 gauge spinal needle, taking all aseptic precautions[30], while the animals were in a standing position. After administration of the drug/s, the animals were left undisturbed until the onset of the drug effect. Analgesia, sedation and motor incoordination were evaluated at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min. In all the animals the same persons, who were blinded to the treatment given, recorded the observations.

Analgesia at the base of the tail, perineum (mid-way between anus and scrotum/udder), hind limbs (coronary band of the digit), flank (paralumbar fossa) and thorax (10th rib) was assessed by recording the response to a pin prick using a hypodermic needle (24 gauge) and graded

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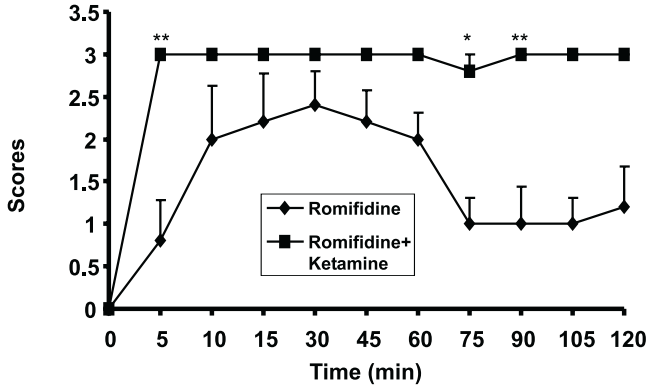

Fig.1: **Score** (mean ± SE) **for analgesia at perineum after intrathecal administration of romifidine or romifidine and ketamine in goats. ***Significantly different between groups at *($P < 0.05$) and **($P < 0.01$).**

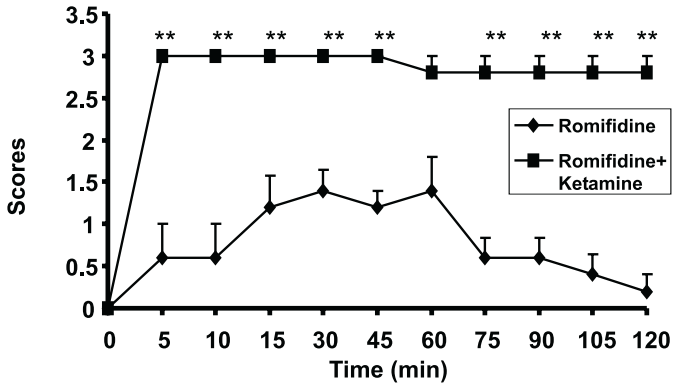

Fig. 2: **Score** (mean ± SE) **for analgesia at tail after intrathecal administration of romifidine or romifidine and ketamine in goats.**

as: 0, no analgesia, *i.e.* strong response to pin prick; 1, mild analgesia, *i.e.* moderate response to pin prick; 2, moderate analgesia, *i.e.* weak to very weak response to pin prick; and 3, complete analgesia, *i.e.* complete abolition of response to pin prick.

Motor incoordination of hind limbs was assessed by making the animal stand or walk, and graded as: 0, no incoordination; 1, slight incoordination; 2, moderate incoordination, where the animal was able to walk without support; 3, severe incoordination, where the animal was unable to stand without support, assuming either sternal or lateral recumbency.

Sedation assessed by general attitude, response to noise, drowsiness and drooping of the head and was scored as: 0, no sedation; 1, mild sedation; 2, moderate sedation; and 3, severe sedation.

Heart rate (HR, beats/min), respiratory rate (RR, breaths/min) and rectal temperature (RT, °C) were recorded just before administration of any drug and at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120–min after intrathecal drug administration. The animals were also observed for salivation, urination and any other untoward reaction during the entire period of study.

Five mℓ of venous blood was collected from the jugular vein in all the animals at 0, 30, 60 and 120 min after drug administration. About 1 mℓ of blood from each sample was used to determine packed cell volume (PCV) and haemoglobin (Hb). Plasma was separated and used to estimate total proteins and albumin (Modofied Biuret and Dumas method[45]), globulin and A:G ratio, glucose (GOD/POD method[43]), urea nitrogen (DAM method[31]) and creatinine (alkaline picrate method[29]).

In the second phase of the experiment, 4 animals from each group were randomly chosen and again divided randomly in 2 equal groups, I and II. The parameters studied in this phase included mean arterial pressure (MAP), central venous pressure (CVP) and electrocardiogram (ECG). For this purpose, the animals were secured in right lateral recumbency and the left lateral region of the neck was prepared aseptically. Under local infiltration analgesia (using 2 % lignocaine HCl), the carotid artery and jugular vein were catheterised using disposable plastic catheters. The carotid catheter was connected to an aneroid manometer to record arterial pressure. The jugular catheter was advanced up to the level of right atrium and connected to a water manometer to record the CVP. A lead II ECG was recorded (Cardiart-308, BPL India) at 1 mV and 25 mm/s paper speed. After stabilising the animals for at least 15 min, the base values of MAP (kPa), CVP (cm H_2O) and ECG were recorded. Thereafter, with the animals in lateral recumbency, the drug/s were injected into the lumbosacral subarachnoid space in both groups, taking all aseptic precautions. The drugs and their dosage used were the same as in first phase of the study. After drug administration, MAP, CVP and ECG were recorded at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min. The ECG was analysed for the duration, amplitude and rhythm of different components.

Statistical analysis

The data for objective parameters such as HR were analysed using one-way analysis of variance for comparison of means between the groups at corresponding intervals and the paired *t*-test was used to compare the means at different intervals to their base values within the group. Subjective observations were tested by Wilcoxon's Signed-rank test[40]. The data were presented as the mean ± SE. The significance was accepted at $P < 0.05$.

RESULTS

Onset of analgesia was observed 5.2 ± 0.54 min following intrathecal administration of romifidine in group I, whereas the onset of analgesia was significantly ($P < 0.01$) earlier in group II (35.5 ± 6.25 s) where romifidine and ketamine were co-administered. Analgesia first appeared in the perineum and later spread cranially towards the hind limbs and flank in both groups.

Analgesia of the perineum varied from mild to moderate in group I (Fig. 1). Moderate analgesia was recorded from 10–60 min, thereafter, mild analgesia persisted up to 120 min. In group II, almost complete analgesia was recorded from 5 min until the end of the observation period, but it was significantly ($P < 0.05$) greater than that of group I only at 5, 75 and 90 min. Tail analgesia varied from mild to moderate in group I, but it was complete and significantly ($P < 0.01$) greater in group II (Fig. 2). Analgesia of the hind limbs and flank was generally moderate in group I, and the peak effect was seen at 30 min (Figs 3, 4). In group II, complete analgesia was observed in the hind limbs (5–120 min), and it was significantly ($P < 0.05$) greater than that of group I throughout the period of observation. Analgesia of the flank was generally moderate, except from 15 to 30 min, during which time complete analgesia was observed in group II. Only mild analgesia of the thorax was recorded in group I (peak effect at 30 min). In group II, however, moderate to complete analgesia was recorded from 15 to 60 min, and the difference was significant ($P < 0.05$) at 15 and 45 min intervals. Moderate to mild analgesia persisted up to 120 min (Fig. 5).

Three animals in group I showed mild incoordination after 15 min of intrathecal romifidine injection (group I) that persisted up to 120 min. All the animals remained standing throughout the period of observation (Fig. 6). Two animals did not show any sign of ataxia/motor incoordination. Animals of group II showed moderate to complete hindquar-

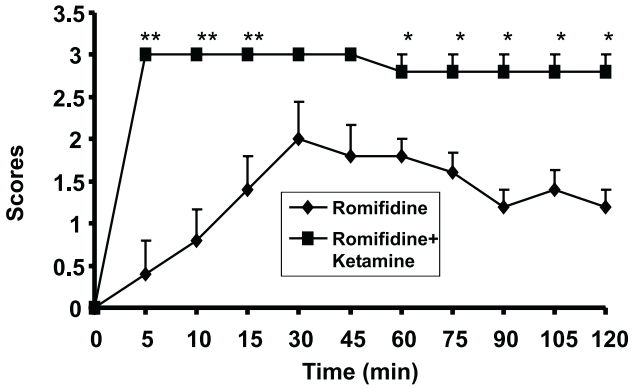

Fig. 3: **Score** (mean ± SE) **for analgesia at hind limbs after intrathecal administration of romifidine or romifidine and ketamine in goats. *'**Significantly different between groups at *($P < 0.05$) and **($P < 0.01$).**

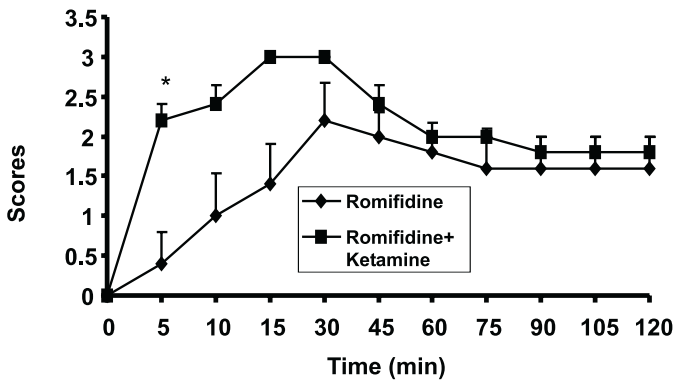

Fig. 4: **Score** (mean ± SE) **for analgesia at flank after intrathecal administration of romifidine or romifidine and ketamine in goats. *'**Significantly different between groups at *($P < 0.05$) and **($P < 0.01$).**

ter weakness from 5 min till the end of observation period, and only 1 animal could stand throughout the period. Motor incoordination was significantly ($P < 0.05$) greater in group II than that in group I up to 90 min of observation.

Sedation was mild to moderate in both groups (maximum effect seen between 30 and 60 min), although it was more consistent in group II (Fig. 7). However, there were no significant differences in the scores for sedation between the 2 groups.

Salivation occurred in both groups, but no difference was seen between the groups. Urination also occurred in all the animals of both groups. No other untoward reaction was seen, and all the animals recovered uneventfully.

The effects of intrathecal romifidine (group I) and romifidine and ketamine (group II) on HR, RR and RT are presented in Table 1. Heart rate decreased significantly ($P < 0.01$) in both groups from 5 min onwards after the intrathecal injections. However, in contrast to group I, the values in group II started to return towards the baseline at the end of observation period. Transient reduction in RR was recorded in group I, which was statistically significant ($P < 0.05$) at 10, 15 and 60 min. By contrast, the animals in group II showed significant and more prolonged reduction in RR from 10 to 120 min. Rectal temperature increased slightly in group I from 5 min onwards till the end, while group II showed a transient increase in RT, followed by reduction at the end. The changes in RT, however, were insignificant in both groups.

Mean arterial pressure reduced significantly ($P < 0.05$) in group I from 5 to 15 min (Fig. 8), whereas in group II, no marked change in MAP was seen, except for an insignificant reduction for a brief period at 60 min of drug injection. However, MAP returned to near baseline level in both groups at the end of observation period. Central venous pressure increased significantly ($P < 0.05$) soon after drug administration in both groups (Fig. 9). In group I, CVP increased sharply compared to group II, but later (after 30 min) reduced slightly. However, in both groups, CVP remained high until the end of observation period.

ECG changes included bradycardia, increased PR and QT intervals and increased amplitude of the T-wave in both groups. Biphasic and inverted T-wave was observed in 1 animal each in group I, and sinus arrhythmia and second degree atrio-ventricular (A-V) conduction block was recorded in another animal in group II.

Plasma biochemical and haematological changes in goats after the intrathecal administration of romifidine and ketamine are given in Table 2. Plasma glucose increased significantly ($P < 0.01$) from 30–120 min in both groups, but no marked difference was seen between the groups. Total proteins did not show any significant change in either group at any stage of observation. However, a significant ($P < 0.05$) reduction in albumin and an increase in globulin levels were recorded in group II at the 30 min interval. Baseline values of plasma nitrogen varied significantly between the 2 groups, but no significant change was observed after the intrathecal injections in both groups. Similarly, the creatinine level did not change significantly in either group at any stage of observation.

Haematological parameters such as Hb and PCV did not vary significantly following intrathecal injections of romifidine alone or in combination with ketamine in either group.

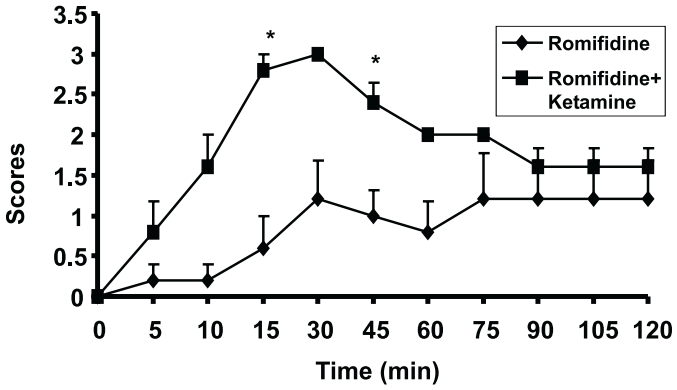

Fig. 5: **Score** (mean ± SE) **for analgesia at thorax after intrathecal administration of romifidine or romifidine and ketamine in goats. *Significantly different ($P < 0.05$) between groups.**

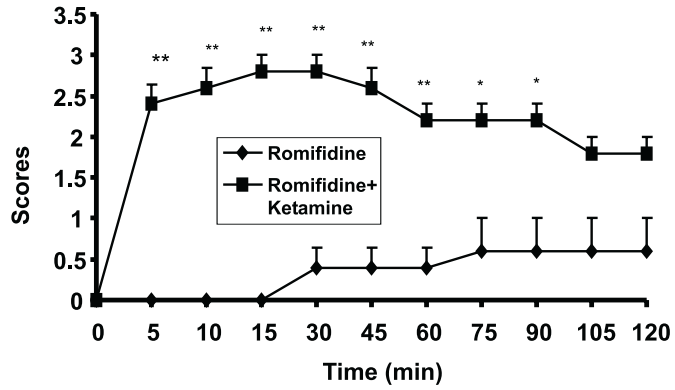

Fig. 6: **Score** (mean ± SE) **for motor incoordination after intrathecal administration of romifidine or romifidine and ketamine in goats. *'**Significantly different between groups at *($P < 0.05$) and **($P < 0.01$).**

Table 1: **Mean** (±SE) **values of heart rate, respiratory rate and rectal temperature in goats after intrathecal administration of romifidine** (group I)**, and romifidine and ketamine** (group II)**.**

Parameters	Group	Time (min)										
		0	5	10	15	30	45	60	75	90	105	120
HR (beats/min)	I	77.8 ± 4.7	64.0 ± 4.2**	58.0 ± 3.7**	50.0 ± 3.2**	50.4 ± 3.0**	48.8 ± 2.0**	49.6 ± 2.4**	51.2 ± 2.3**	52.8 ± 2.3**	49.2 ± 2.0**	49.6 ± 2.1**
	II	78.0 ± 4.4	66.4 ± 4.4	55.0 ± 4.4*	50.4 ± 4.2**	46.2 ± 3.0**	47.4 ± 2.8**	46.6 ± 2.6**	53.4 ± 3.3**	49.0 ± 3.1**	55.0 ± 1.7**	58.0 ± 2.1*
RR (breaths/min)	I	22.4 ± 1.6	16.6 ± 2.1[a]	14.6 ± 1.0*	13.0 ± 2.7*	16.2 ± 3.3	15.6 ± 1.9	13.4 ± 0.8*	14.2 ± 1.5	15.6 ± 1.4	18.2 ± 2.1[a]	18.8 ± 1.8
	II	27.4 ± 0.6	25.0 ± 1.5[b]	15.6 ± 1.6**	15.6 ± 1.9**	15.8 ± 2.9*	13.6 ± 2.1**	12.8 ± 1.5**	14.6 ± 3.1*	12.4 ± 1.6**	12.6 ± 1.4**[b]	13.2 ± 1.2**
RT(°C)	I	38.9 ± 0.1	39.1 ± 0.1	39.2 ± 0.1	39.2 ± 0.1	39.3 ± 0.2	39.3 ± 0.2	39.2 ± 0.3	39.1 ± 0.3	39.2 ± 0.3	39.2 ± 0.4	39.2 ± 0.4
	II	38.9 ± 0.2	39.1 ± 0.2	39.1 ± 0.2	39.1 ± 0.2	39.1 ± 0.2	38.9 ± 0.2	38.8 ± 0.2	38.8 ± 0.2	38.6 ± 0.2	38.5 ± 0.1	38.5 ± 0.1

*,**Significantly different from baseline value at *($P < 0.05$) or **($P < 0.01$).
[a,b]Values with different superscript letters differ significantly ($P < 0.05$) between groups at corresponding intervals.
HR = heart rate, RR = respiratory rate, RT = rectal temperature.

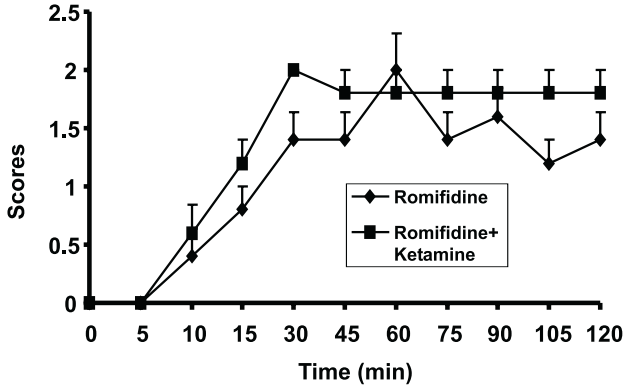

Fig. 7: **Score** (mean ± SE) **for sedation after intrathecal administration of romifidine or romifidine and ketamine in goats. Values do not differ significantly (*P* > 0.05) between groups.**

DISCUSSION

Analgesia

Romifidine has been reported to produce various degrees of analgesia after systemic administration in horses[16,21] and goats[36]. The results of the present study in group I indicated that romifidine can produce mild to moderate degrees of hindquarter analgesia after intrathecal administration. Alpha-2 adrenoceptor agonists such as xylazine have been shown to stimulate alpha-2 adrenoceptors at the spinal cord level, thereby inhibiting the release of neurotransmitters and decreasing neuronal activity[26,28]. The mechanism of analgesic action of intrathecally administered romifidine, like that of other alpha-2 adrenergic agonists, was probably due to stimulation of alpha-2 adrenoceptors at the spinal cord level. In the present study, the onset of analgesia after intrathecal injection of romifidine was observed within 5.2 ± 0.54 min. This effect was a somewhat shorter than that seen after intrathecal administration of xylazine (0.05 mg/kg) and medetomidine (10 µg/kg) in goats (9–10 min)[22]. However, the extent and duration of analgesia with intrathecal romifidine (group I) was almost similar to that seen with xylazine or medetomidine in that study. In group II, where romifidine and ketamine were co-administered, the onset of analgesia was decreased (35.5 ± 6.25 s) compared to group I. The analgesia was also more intense and complete in this group, indicating the role of ketamine in increasing analgesia obtained from romifidine. When ketamine alone was administered epidurally and intrathecally, it has been shown to produce varied degree of hind quarter analgesia of short duration in different species of domestic animals[1,2,22]. Ketamine is known to act as a non-competitive antagonist of NMDA receptors, which are involved in the transmission and modulation of nociceptive information at the spinal cord level[46]. Previous studies have demonstrated potentiation of the analgesic effects of xylazine and medetomidine after epidural or intrathecal administration along with ketamine in goats[1,22], dogs[23] and calves[3], through synergistic interaction. In the present study, rapid and complete hindquarter analgesia of a long duration was recorded in group II, suggesting possible synergistic interaction between spinally administered romifidine and ketamine.

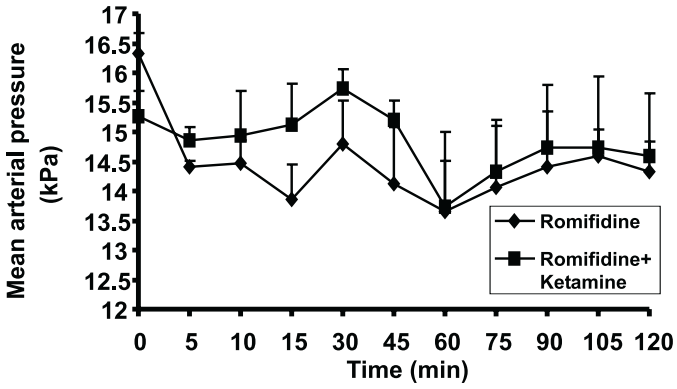

Fig. 8: **Mean** (±SE) **arterial pressure after intrathecal administration of romifidine or romifidine and ketamine in goats. Values do not differ significantly (*P* > 0.05) between groups.**

Table 2: **Mean** (±SE) **values of plasma biochemical and haematological parameters in goats after intrathecal administration of romifidine** (group I)**, and romifidine and ketamine** (group II)**.**

Parameters	Groups	Intervals (min)			
		0	30	60	120
Glucose (mmol/ℓ)	I	03.1 ± 0.3	09.0 ± 0.4**	10.7 ± 0.9**	12.1 ± 2.4**
	II	02.6 ± 0.3	08.3 ± 0.2**	09.2 ± 0.2**	08.8 ± 0.4**
Total proteins (mmol/ℓ)	I	67.9 ± 0.6	68.2 ± 0.3	68.4 ± 0.5	67.7 ± 0.5
	II	67.7 ± 0.2	67.7 ± 0.2	67.7 ± 0.2	68.3 ± 0.4
Albumin (mmol/ℓ)	I	37.1 ± 1.4	36.2 ± 0.6	35.5 ± 1.1	36.4 ± 0.8
	II	33.6 ± 0.8	31.0 ± 0.6*	31.9 ± 0.4	31.0 ± 1.2
Globulin (mmol/ℓ)	I	30.8 ± 1.7	32.0 ± 0.8	32.9 ± 1.4	31.3 ± 0.6
	II	34.1 ± 0.9	36.7 ± 0.6*	35.8 ± 0.5	37.3 ± 1.2*
A:G	I	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.0
	II	1.0 ± 0.1	0.8 ± 0.0*	0.9 ± 0.0	0.8 ± 0.1*
Plasma urea nitrogen (mmol/ℓ)	I	12.7 ± 0.8	11.7 ± 1.4	11.2 ± 1.2	13.6 ± 0.9
	II	7.8 ± 0.7	8.5 ± 0.5	8.9 ± 0.9	8.3 ± 0.4
Creatinine (µmol/ℓ)	I	174.8 ± 6.0	183.0 ± 6.9	170.5 ± 6.3	178.2 ± 5.6
	II	174.1 ± 1.7	179.2 ± 5.0	175.3 ± 2.8	168.3 ± 2.3
Haemoglobin (g%)	I	10.3 ± 0.5	09.9 ± 0.3	09.7 ± 0.5	09.5 ± 0.5
	II	09.9 ± 0.5	10.2 ± 0.6	09.9 ± 0.2	09.6 ± 0.3
PCV (%)	I	33.8 ± 0.6	33.6 ± 1.7[a]	31.5 ± 1.0[a]	31.2 ± 0.9*[a]
	II	30.3 ± 0.5	29.5 ± 0.6[b]	30.0 ± 0.7[b]	29.3 ± 0.8[b]

*/**Significantly different from baseline value at *($P < 0.05$) or **($P < 0.01$).
[a,b]Values with different superscript letters differ significantly ($P < 0.05$) between groups at corresponding intervals.

In both groups, analgesia first appeared at the perineum and tail, and later spread cranially towards the flank. The extent and duration of analgesia was also greater for the perineum than the hind limbs or flank. This may be due to early spread of a large quantity of the drug towards the sacrococcygeal region after injection at the lumbosacral subarachnoid space in standing goats. Furthermore, it may suggest a possible high concentration of alpha-2 adrenoceptors in the caudal part of the spinal cord, although the density of alpha-2 adrenergic receptors in the various segments of spinal cord of different animal species is unknown[38]. However, in humans, the density of alpha-2 adrenoceptors is apparently greater in the sacral part of spinal cord than the lumbar or thoracic parts[27].

Motor incoordination

Various degrees of ataxia and motor incoordination have been reported in goats after epidural and intrathecal injections of alpha-2-adrenergic agonist drugs such as xylazine[1,22]. The degree of motor incoordination was generally dose dependent. Some degree of ataxia and motor incoordination recorded in a few animals injected with intrathecal romifidine in the present study indicated a local anaesthetic like action of romifidine, similar to other alpha-2-adrenergic agonists such as xylazine. Butterworth and Strichartz[11] have speculated that the local anaesthetic action of alpha-2-adrenergic agonists affects both A- and C-fibres, with the C-fibres being more potently inhibited than A-fibres. Higher concentrations of drugs would probably be required to inhibit A-fibres leading to motor block, and this may explain why only mild ataxia/motor incoordination was recorded in group I. The degree of motor incoordination seen in this group was comparable to that reported in goats injected with intrathecal xylazine/medetomidine[22]. LeBlanc *et al.*[28] have reported indiscriminate blockade of sensory, motor and sympathetic nerves by an alpha-2-adrenergic agonist drug. In the present study, motor incoordination was observed much later (15 min after romifidine injection) than the appearance of analgesia, suggesting that sensory fibres were blocked sooner than motor fibres. In group II, motor incoordination was severe with a faster onset, indicating possible additive or synergistic effects of romifidine and ketamine, similar to that seen with ketamine and xylazine/medetomidine[22]. Ketamine is also known to cause local anaesthesia after intrathecal and intravenous regional injections[6,9]. The higher degree of motor block seen in group II could be attributed to local anaesthetic action of ketamine at spinal nerve roots.

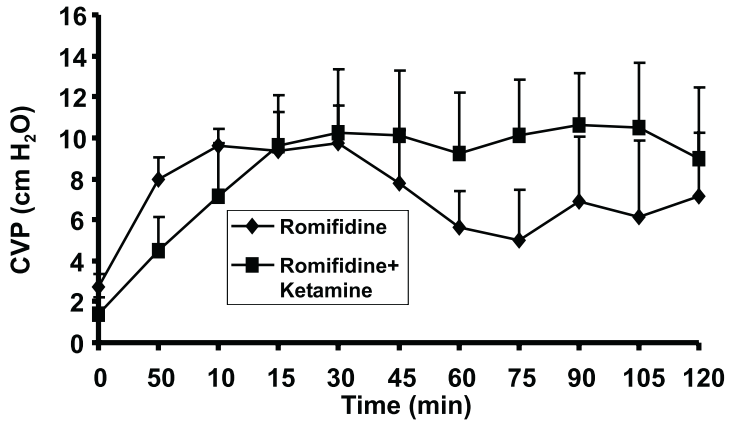

Fig. 9: **Central venous pressure** (cm H_2O) **after intrathecal administration of romifidine or romifidine and ketamine in goats. Values do not differ significantly ($P > 0.05$) between groups.**

Sedation

Mild to moderate sedation was induced about 10–15 min after intrathecal administration of romifidine, indicating that the drug was rapidly absorbed from the subarachnoid space and distributed to supraspinal centres. Similar effects have been reported after epidural or intrathecal injections of xylazine or mede-

tomidine in goats[1,22]. The sedative effect of alpha-2 adrenergic agonists is associated with the activation of alpha-2 adrenoceptors causing a decrease in the release and turnover of noradrenaline in the central nervous system (CNS)[37]. The degree of sedation in group II remained almost the same in comparison to group I, indicating that ketamine probably did not contribute to sedation. This agrees with previous studies, where ketamine at a dose of 2.5 mg/kg body weight failed to induce sedation after epidural or intrathecal injections in goats[1,22]. In association with sedation, mild salivation was also recorded in animals of both groups.

All the animals in both groups urinated about 60 min after the intrathecal drug injection, which is a common finding with alpha-2-adrenergic agonists[1,22]. Urination is attributed to inhibition of production and release of anti-diuretic hormone (ADH)[12], and the hyperglycemic effect of alpha-2 adrenergic agonist drugs[15,19], as also observed in the present study, leading to osmotic diuresis.

Heart rate

Alpha-2-adrenergic agonists such as xylazine/medetomidine have been reported to decrease the heart rate in goats, cattle and horses following epidural or intrathecal injections [1,3,24,37]. In the present study, a significant reduction in HR was also noticed soon after intrathecal injection of romifidine until the end of the observation period in group I. Romifidine has also been shown to reduce the HR after systemic administration in horses and goats[16,21,36]. Bradycardia could be attributed to decreased sympathetic outflow from the CNS, direct depression of cardiac pacemaker and conduction tissues and increased vagal tone[37]. Group II also showed a significant reduction in HR. However, at the end of observation period, the HR started to return towards the base line rates, which is in contrast to that of group I. This may be attributed to the presence of ketamine, a positive chronotrophic drug. This observation was in agreement with earlier studies with intrathecal/epidural injections of ketamine with xylazine/medetomidine in goats[1,22], dogs[23] and calves[3].

Respiratory rate

Respiratory rate was significantly reduced after intrathecal injection of romifidine in group I, as also reported after its systemic administration in goats and dogs[4,17,36]. Epidurally- or intrathecally-administered alpha-2-adrenergic agonists have been reported to cause reduction in RR and irregular respiration in different species of animals[1,3,22,23,37]. Respiratory effects of intrathecally/epidurally administered alpha-2 agonists are said to be mediated through alpha-2 adrenoceptor activity or/and depression of respiratory centre[37]. In this study, reduction in RR was transient in group I, whereas in group II, significant reduction in RR was observed throughout the period of observation. This could be attributed to additive effects of ketamine and romifidine. Ketamine has been reported to cause either a decrease or an increase in RR in different animal species. However, the changes in RR observed in group II were somewhat different from those observed in earlier studies with epidural/intrathecal injections of ketamine with xylazine or medetomidine[1,22].

Rectal temperature

Contrasting findings have been reported about the changes in body temperature following epidural/intrathecal injection of alpha-2-adrenergic agonists. Hypothermia was reported in cats, sheep and goats after the use of xylazine/medetomidine[1,5,22,34], and it has been attributed to generalised sedation, decreased metabolic rate, muscular relaxation and depression of the hypothalamus. By contrast, an increase in RT has been reported in cattle after epidural injection of xylazine[37,41], and the authors did not comment on possible causes for the hyperthermia. In the present study, there was an increase in RT (although insignificant) in both groups. This change in RT may not necessarily reflect the change in body temperature. The RT remained elevated throughout the observation period in animals of group I, whereas in group II animals an initial increase was followed by a reduction, to remain below normal temperature at the end. The decline in RT started at 45 min suggesting that subsequent decrease in RT was possibly attributed to CNS depression. The depression of CNS was probably greater in this group of animals due to the combined effects of romifidine and ketamine. Changes in RT in group II animals were almost similar to that observed in goats injected with epidural xylazine and ketamine[1].

Mean arterial pressure

Romifidine (group I) produced a significant reduction in MAP, similar to other alpha-2-adrenergic agonists used in goats[24]. Epidurally/intrathecally-administered alpha-2-adrenergic agonists have been shown to reduce the arterial blood pressure through both spinal and central actions of the drug[32,47]. Hypotension is attributed to stimulation of alpha-2 adrenoceptors, peripheral sympatholytic action and enhanced parasympathetic outflow[33,42]. Bradycardia and vasodilatation produced by these drugs may also contribute to hypotension[35]. Hypotension has also been reported after systemic injection of romifidine in goats[36]. In the present study, MAP returned to the baseline well before the end of observation period, although HR remained significantly lower during the same period. This indicated that a compensatory mechanism of the cardiovascular system was activated to maintain the system and romifidine did not affect the cardiovascular function adversely. In group II, MAP was only insignificantly reduced in the early period. The addition of ketamine in this group counteracted the hypotensive effect of romifidine to some extent. The positive inotropic effect of ketamine on the heart probably helped to maintain cardiac output. Similar effects have been observed after epidural/intrathecal administration of ketamine with xylazine or medetomidine in goats[1,22].

Central venous pressure

Intrathecal injection of both romifidine and romifidine-ketamine combination produced significant increase in CVP. The increase in CVP was probably due to pooling of blood in the venous circulation as a result of decreased HR and depression of cardiac function[44]. Central venous pressure remained significantly high till the end, but it tended to decrease at the end, suggesting gradual elimination of the depressant effect and activation of compensatory mechanisms to return the CVP to baseline pressure. Increased CVP has also been reported after intrathecal administration of xylazine or medetomidine alone or in combination with ketamine in goats[22,24]. Romifidine also increased CVP after its systemic injection in goats[36].

Electrocardiogram

Increased PR and QT intervals and increased amplitude of the T-wave in the ECG recorded in the present study were similar to those reported earlier after epidural/intrathecal injections of alpha-2 agonists in different species of animals including goats[24]. Increase in PR and QT intervals may suggest decreased conduction velocity within the atrium and ventricles, respectively[44]. It may also be due to decrease in HR. Increase in the amplitude of the T-wave may indicate myocardial hypoxia. Sinus arrhythmia and second degree A-V conduction block seen in a few animals could be attributed to increased vagal activity caused by the vasopressor effects of alpha-2-agonists[25].

However, there was no difference in ECG changes between the two groups.

Biochemical parameters

Plasma glucose levels increased significantly ($P < 0.01$) in both groups (Table 2). Similar effects have been reported after the administration of alpha-2 agonists in different species of animals[10,12,15,19]. The hyperglycaemic effect of alpha-2 agonists is probably due to stimulation of alpha-2 receptors in the pancreatic β-cells leading to inhibition of insulin release[7]. It may also be due to an increased production of glucose in the liver[19] or a rise in adrenocortical hormones due to stress. In the present study, however, no significant difference was seen between the groups. Total proteins did not vary much in either group. In group I, insignificant reduction in albumin and increase in globulin was noted, whereas in group II, reduction in albumin and increase in globulin were significant ($P < 0.05$) at the 30 min interval. Changes in plasma urea nitrogen and creatinine were not significant in either group, similar to the effects of intrathecal xylazine/medetomidine injections in goats[22].

Decrease in PCV, Hb and total leukocyte count have been reported after epidural or intrathecal injections of xylazine/medetomidine in goats and other species of animals[22,41]. Decrease in PCV and Hb was attributed to decreased sympathetic activity after injection of alpha-2 agonists, leading to pooling of circulating erythrocytes in the spleen or other reservoirs[39]. However, in the present study, no significant change was seen in PCV and Hb values in both groups.

CONCLUSION

From the results of this study, it is concluded that spinal administration of romifidine (50 µg/kg) produced mild to moderate hindquarter analgesia in goats. The effects were similar to that produced by intrathecal injections of xylazine (0.05 mg/kg) or medetomidine (10 µ g/kg). Addition of ketamine (2.5 mg/kg) to romifidine (50 µg/kg) produced complete hindquarter analgesia of prolonged duration suggesting possible synergistic interaction between spinally administered romifidine and ketamine. The interaction did not result in systemic side-effects. Hence, the combination of romifidine and ketamine can be safely used to produce hindquarter analgesia in surgery involving the perineum, tail, hind limbs, udder and flank in goats.

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