ORIGINAL ARTICLE

Comparative evaluation of the sedative and physiological effects of medetomidine alone and in combination with pethidine, morphine, tramadol, and methadone in goats

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Abstract

Background: The use of combinations of α_2-adrenergic agonists and opioids has been published as providing superior sedation than either drug alone.

Introduction: The present study aims to compare the sedative and physiological effects of intravenous (IV) administration of medetomidine alone and in combination with methadone, morphine, tramadol, and pethidine in goats.

Methods: Ten healthy goats aged 12 ± 3 months and weight of 22 ± 4 kg were used in an experimental, crossover (Latin square), randomized, and blinded study. The animals were assigned to five IV treatments with a minimum washout period of 8 days between treatments: medetomidine (20 μg kg^{-1}), medetomidine/methadone (0.5 mg kg^{-1}), medetomidine/morphine (0.5 mg kg^{-1}), medetomidine/tramadol (5 mg kg^{-1}), and medetomidine/pethidine (1 mg kg^{-1}).

Results: Clinical adverse effects such as tremors (facial and generalized), bruxism, nystagmus, mydriasis, and vocalization were presented in all the medetomidine/opioid treatments. Clinical adverse effects were observed at 10–90 minutes in medetomidine/opioid treatments. Animals in all treatments were sedated at 5–90 minutes. Sedation was significantly higher in medetomidine/opioid treatments than in medetomidine at 15–30 minutes after administration ($P < 0.05$). In all treatments, heart rate and respiratory rate significantly decreased from baseline at 5–105 and 30–60 minutes, respectively. There was no significant difference in heart and respiratory rates between different treatments at any time point. Ruminal motility was decreased in medetomidine and medetomidine/opioid treatments at 10–75 and 10–105 minutes, respectively. Compared with medetomidine, ruminal motility was significantly lower in medetomidine/opioid treatments at 75–105 minutes.

Conclusion: The use of combinations of medetomidine/opioids would be considered for superior sedation at 15–30 minutes after administration in goats. No significant differences were detected among opioids in combination with medetomidine in goats.

1 | INTRODUCTION

In addition to physical restraint, chemical agents are useful and often necessary to ensure immobility and to provide sedation and analgesia for surgical and nonsurgical procedures in veterinary patients (Borges et al., 2016; De Carvalho et al., 2016; Pawde et al., 1996). Many α_2-agonists and narcotics are commonly used for sedation and antinociception in ruminants (Ajadi et al., 2012; Kalhoro & Memon, 2011; Olsen et al., 2013). The use of combinations of α_2-adrenergic agonists and opioids has been published as providing superior sedation to either drug alone in sheep (Borges et al., 2016; De Carvalho et al., 2016). However, the reported use of these drugs in goats is rare.

Opioids are widely used to relieve mild to severe pain. These drugs are not used routinely in veterinary patients, because substantial sympathetic stimulation and central nervous system (CNS) excitation are observed when opioids are administered (Borges et al., 2016; Cardoso et al., 2014). Other clinical adverse effects of opioids may include respiratory depression and gastrointestinal problems (such as ileus, impaction, and obstruction). In addition, narcotics such as methadone, morphine, pethidine, and tramadol are potent locomotor stimulants (Riviere & Papich, 2017). Studies on the sedative and analgesic effects of opioids are lacking, which may limit the clinical usefulness of opioids in goats.

As there is a distinct lack of documented information on the sedative effects of α_2-adrenergic agonists in combination with opioids in goats, the present study aimed to compare the effects of intravenous (IV) administration of medetomidine alone and in combination with morphine, methadone, tramadol, and pethidine on sedation and physiological variables in goats. The hypothesis of this study is that the sedative and physiological effects in goats would vary between opioids in combination with medetomidine in goats. The results of this study would be really clinically useful for veterinary practitioners.

2 | MATERIALS AND METHODS

2.1 | Animals

The study was approved by the animal welfare committee of the Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman (IR.UK.VETMED.REC.1399.023). Ten goats were used for the study with a mean age of 12 ± 3 [mean $\pm$ standard deviation (SD)] months and weight of 22 ± 4 kg. The animals were selected from the Animal Husbandry Unit of Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman (IR.UK.VETMED.REC.1399.023) using a sample lottery method (simple randomization). All animals were housed under the same environmental, nutritional, and management conditions in a same

group pen. The goats received constant mixture containing roughages (mainly alfalfa hay and wheat straw) and concentrate (barley grain, soybean meal, wheat bran) based on physiological maintenance during the experiment. The forage/concentrate ratios during the experiment were 90:10. Enough vitamins, minerals, and fresh water were also provided. Two months before the experiment, animals were treated with broad-spectrum antiparasitic drugs for probable internal and external parasitic infestation. Health status of all animals was checked routinely by clinical (including heart and respiratory rate (HR and RR), rectal temperature (RT), capillary refill time (CRT) and ruminal motility) and paraclinical examinations. The paraclinical examination consisted of hematological (evaluation of complete blood count and packed cell volume) and fecal parasitic analysis.

Two days before the start of the study, they were checked for normal health status using clinical and paraclinical evaluations. Prior to the experiment, food and water were withheld from the animals for 12 and 6 hours, respectively. The experiment was carried out in the morning. The animals were weighed before each treatment for calculation of drug dosages. Two animals were studied at any one time. The animals were unable to see each other. The animals were gently restrained on the special bed (on top of a soft mattress) in a quiet, covered, 5×6 m^2 area and rested for 20 minutes before first measurement of physiological variables were recorded. The skin over the left jugular vein was prepared aseptically for IV administration. Clinical and paraclinical examinations were repeated 48 hours after the experiment to evaluate the health status of the animals.

2.2 | Experimental procedures

The goats were assigned to five IV treatments in a randomized (computer-generated) crossover Latin square design with a minimum washout period of 8 days between treatments. Treatments were included: MED, medetomidine (20 μg kg $^{-1}$; DorbeneVet; N-Vet AB, Sweden); MME, MED, and methadone (0.5 mg kg^{-1}; Faran Chimi Pharmaceutical Company, Iran); MMO, MED, and morphine (0.5 mg kg^{-1}; Dimorf; Cristália Produtos Químicos e Farmacêuticos Ltda); MTR, MED, and tramadol (5 mg kg^{-1}; Tehran Chime Pharmaceutical Company, Iran); and MPE, MED, and pethidine (1 mg kg^{-1}; Caspian Tamin Pharmaceutical Company, Iran). Each drug combination was mixed in the syringe. The injection volumes of treatments were the same for each animal by dilution with 0.9% saline (Shahid Ghazi Pharmaceutical Company, Tabriz, Iran) to 5 mL. Treatments were administered IV in the left jugular vein (over 2 minutes) through an 18-gauge needle with the animals standing and then the animals were left alone. All injections were recorded as being smooth with no obvious extravasation of the drug. The person who injected each time was the same. All

investigators recording measurements were unaware of the treatment assigned.

2.3 | Sedation scores

Three independent observers (who were unaware of the drug type and dose) assessed the degree of sedation for each animal. The degree of sedation was investigated using a numerical ranking scale of 0–10, as follows: 0, no sedation; 1, standing, conscious, decrease head and ear movements; 2, standing, mild head drop; 3, standing, moderate head drop; 4, standing, severe head drop, incoordination; 5, standing, severe head drop, severe incoordination; 6, sternal recumbency, head up; 7, sternal recumbency, head down; 8, lateral recumbency, occasional attempts to attain sternal recumbency; 9, lateral recumbency, uncoordinated movements; and 10, lateral recumbency, no movements (Borges et al., 2016; De Carvalho et al., 2016; Kästner et al., 2003). The final sedation score for each animal was considered the majority score which the observers gave to each animal. Sedation scores were recorded before other measurements at the following times: baseline (before drug administration, time 0) and at 5, 10, 15, 30, 45, 60, 75, 90, and 120 minutes, resulting in 10 time points for each animal. Evaluation of the clinical adverse effects (drooling, bruxism, nystagmus, mydriasis, vocalization, facial and generalized tremors, and urination) was performed at the same time points.

2.4 | Physiological variables

Physiological variables including HR, RR, RT, CRT, and ruminal motility were recorded at the same time points as the sedation was recorded. HR and RR were assessed using veterinary stethoscope (Classic SE Littmann; 3 M, MN, USA) on the left fourth and sixth intercostal space, respectively, for 1 minute. Ruminal motility was recorded by auscultation with a stethoscope placed on the left flank. The number of audible rumen contractions within 2 minutes was counted. CRT was measured by finger pressing on the labial surface of gingiva in the incisor region. A digital thermometer (FT09; Beurer GmbH, Germany) was used to performed RT. Thermometer was 4—5 cm deep in touch with rectal mucosa for at least 2 minutes (Constable et al., 2017).

2.5 | Statistical analysis

A prospective power calculation (G*Power Version 3.1.9.2) conducted on the basis of information reported elsewhere (Borges et al., 2016; De Carvalho et al., 2016) determined that a total of ten animals were required (α of 0.05 and β of 0.2) to detect a 10% difference between treatments. Data were analyzed using SPSS software version 20 (SPSS for Windows, SPSS Inc, Chicago, Illinois). Before any statistical analysis, distribution of data was performed for normality using the Kolmogorov–Smirnov test, and normality of data distribution was verified. Sedation scores and physiological variables were expressed as median (range) and mean ± SD, respectively. Sedation scores were compared at each time using nonparametric (Kruskal–Wallis and Mann–Whitney U) tests. The two-relate-samples test with Wilcoxon test type (in nonparametric method) was applied to compare sedation scores at different times from baseline. One-way analysis of variance with the Tukey post hoc test was used to compare mean values of physiological variables at similar times between different treatments. The paired sample t test was applied to compare physiological variables at different times from baseline. The interrater agreement between the investigators (for each treatment) was performed using Cohen's kappa (k) coefficient. The correlations were ranged (very good, $k = 0.81–1.00$; good, $k = 0.61–0.80$; moderate, $k = 0.41–0.60$; fair, $k = 0.21–0.40$ and poor, $k < 0.20$) based on the model set by Altman (1990). A P value of less than 0.05 was considered significant.

3 | RESULTS

All the goats had recovered by 3 hours based on clinical sings such as standing, head up, head and ear movement, consciousness, and responsiveness. The interrater agreement among the observers was very good ($k = 0.92$; $P < 0.05$). The animals had normal health status 48 hours after the study. Clinical adverse effects other than sedation included drooling, bruxism, nystagmus, mydriasis, vocalization, urination, and tremors (facial or generalized) are shown in Table 1. Clinical side effects were observed at 10–90 minutes in MED/opioid treatments. All goats in each treatment were shown clinical adverse effects (in different patterns) at 10–90 minutes after drug administration. Different variables are demonstrated in Table 2. Animals in all treatments were sedated at 5–90 minutes (Table 2). Just one animal in MME, MTR, and MPE achieved sedation score 1 at 105 minutes after drug administration. Sedation was significantly higher in MED/opioid treatments than in MED at 15–30 minutes after administration ($P < 0.05$; Table 2).

In all treatments HR and RR significantly decreased from baseline at 5–105 and 30–60 minutes, respectively. There was no significant difference in HR and RR between different treatments at any time point. Ruminal motility was decreased in MED and MED/opioid treatments at 10–75 and 10–105 minutes, respectively. Compared with MED, ruminal motility was significantly lower in MED/opioid treatments at 75–105 minutes after administration. No significant differences were detected among MED/opioid treatments for ruminal motility. RT was unchanged in any treatment for 120 minutes (Table 2). CRT was less than two seconds at all time points following each treatment. There was no significant difference in CRT between different treatments at any time point.

4 | DISCUSSION

Alph$_2$-adrenergic agonists in combination with opioids are used for sedation in small ruminants. Combination of these drugs had synergistic sedation effect (Borges et al., 2016; De Carvalho et al., 2016). This

TABLE 1 Clinical adverse effects observed in ten goats over 120 minutes in five treatments: MED, medetomidine (20 μg kg^{-1}); MMO, MED, and morphine (0.5 mg kg^{-1}); MME, MED, and methadone (0.5 mg kg^{-1}); MTR, MED, and tramadol (5 mg kg^{-1}); and MPE, MED, and pethidine (1 mg kg^{-1})

Treat-ments	Time points (minutes)										
	Baseline	5	10	15	30	45	60	75	90	105	120
MED	Normal	Normal	Drooling	Drooling	Drooling	Drooling	Drooling Urination	Drooling Urination	Drooling Urination	Normal	Normal
MMO	Normal	Normal	Drooling	Drooling Bruxism Facial tremors	Drooling Bruxism	Drooling Vocalization Bruxism Mydriasis	Drooling Vocalization Bruxism Mydriasis	Drooling Vocalization	Vocalization	Normal	Normal
MME	Normal	Normal	Drooling Bruxism	Drooling Bruxism Mydriasis Nystagmus Facial tremors	Drooling Bruxism Mydriasis Generalized tremors	Drooling Bruxism	Drooling Vocalization Bruxism	Drooling Vocalization	Vocalization Bruxism	Normal	Normal
MTR	Normal	Normal	Drooling Bruxism	Drooling Bruxism Facial tremors Vocalization	Drooling Bruxism	Drooling Urination	Drooling Urination Vocalization	Drooling Vocalization	Bruxism	Normal	Normal
MPE	Normal	Normal	Drooling Bruxism	Drooling Bruxism Facial tremors	Drooling Bruxism Mydriasis	Drooling Bruxism	Drooling Vocalization Bruxism	Drooling Vocalization	Bruxism	Normal	Normal

synergism in sedation facilitates a reduction in the doses of both drugs, thereby reducing the adverse effects associated with each drug when it is administered alone (Borges et al., 2016; De Carvalho et al., 2016). Time to onset and duration of sedation is important to perform clinical procedures (surgical or nonsurgical) efficiently and properly when chemical agents (such as α_2-adregenrgic agonists and narcotics) administered intravenously (Seddighi & Doherty, 2016). The opioids doses used in the present study were determined based on the doses of these drugs used in other studies in small ruminants (Borges et al., 2016; De Carvalho et al., 2016; Dehkordi et al., 2012; Olsen et al., 2013). Opioids act by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract (Habibian et al., 2011; Mir et al., 2000). The pharmacokinetic effects of many drugs such as opioids in goats are poorly understood due to a lack of studies in this species. There are differences in pharmacokinetic variables of opioids in goats as may be expected, leading to subtle variations in the clinical effects (Riviere & Papich, 2017).

Clinical adverse effects such as drooling, tremors (facial and generalized), bruxism, mydriasis, nystagmus, urination, and vocalization were presented in MED/opioid treatments. Goats exhibited neurologic signs of tremors, gnawing, hyperexcitability, and tail-flicking after administration of methadone IV (Olsén et al., 2013). De Carvalho et al. (2016) demonstrated that administration of xylazine in combination with opioids in sheep leads to similar distressed behavior. Sheep exhibited neurologic signs of tremors, mydriasis, urination, nystagmus, bruxism, and vocalization after IV administration of dexmedetomidine/opioids (Borges et al., 2016). The clinical adverse effects observed in the present study may be due to excitatory effects of opioids on the CNS (Olsén et al., 2013; Torad & Hassan, 2018). The mechanisms for CNS excitation are unknown but may be related to cerebral catecholamine release (especially norepinephrine and dopamine) and opiate receptor activation (Riviere & Papich, 2017).

Animals in MED/opioid treatments were sedated at 5–90 minutes in this study. De Carvalho et al. (2016) were reported 105 minutes sedation after IV administration of 0.1 mg kg^{-1} xylazine in combination with opioids (0.5 mg kg^{-1} morphine, 0.5 mg kg^{-1} methadone, and 0.1 mg kg^{-1} tramadol) in sheep. Intravenous administration of 5 μg kg^{-1} dexmedetomidine in combination with opioids (0.15 mg kg^{-1} butorphanol, 0.5 mg kg^{-1} methadone, and 5 mg kg^{-1} tramadol) in sheep was reported to produce sedation lasting 120 minutes (Borges et al., 2016). Alpha$_2$-adrenergic agonists suppress the vasomotor center in brainstem in the CNS, and opioids provide analgesia by antagonizing N-methyl-D-aspartate (NMDA) receptors. Sedation is associated with a decrease in sympathetic outflow from the CNS (Pawde et al., 1996). Based on the results, the use of combinations of medetomidine/opioids has been provided superior sedation to medetomidine alone at 15–30 minutes after administration. De Carvalho et al. (2016) reported similar finding after IV administration of 0.1 mg kg^{-1} xylazine in combination with opioids (0.5 mg kg^{-1} morphine, 0.5 mg kg^{-1} methadone, and 0.1 mg kg^{-1} tramadol) in sheep. In a study carried out in sheep, treatment with 0.5 μg kg^{-1} dexmedetomidine in combination with opioids (0.15 mg kg^{-1} butorphanol, 0.5 mg kg^{-1} methadone, and 5 mg kg^{-1} tramadol) resulted in different sedation score (Borges et al., 2016). In surgical or nonsurgical procedures, which require superior sedation, the combination of α_2-adrenergic agonists with opioids would be considered at 15–30 minutes after administration in goats. It should be noted that variation in drug combination, doses of drugs, sex, age, species and breed, and other parameters including environmental variables may affect the efficiency of sedation in farm practice (Olsén et al., 2013).

TABLE 2 Comparison of medetomidine alone and combination with methadone, morphine, tramadol, and pethidine on sedation scores [median (range)], and physiological variables (mean ± standard deviation) in ten goats. Animals were assigned to five intravenous treatments in a crossover Latin square, randomized (computer-generated), and blind study: MED, medetomidine (20 μg kg⁻¹); MMO, MED, and morphine (0.5 mg kg⁻¹); MME, MED, and methadone (0.5 mg kg⁻¹); MTR, MED, and tramadol (5 mg kg⁻¹); and MPE, MED, and pethidine (1 mg kg⁻¹).

		Time points (minutes)										
Variables	Treatments	Baseline	5	10	15	30	45	60	75	90	105	120
Sedation score (0–10)	MED	0 (0-0)	4 (2-4)†	6 (3-6)†	7 (5-8)†	9 (6-9)†	7 (6-7)†	5 (4-5)†	3 (2-4)†	1 (1-3)†	0 (0-0)	0 (0-0)
	MMO	0 (0-0)	4 (2-4)†	6 (3-6)†	8 (6-9)*†	8 (7-9)†	6 (5-7)†	4 (3-6)†	3 (2-5)†	2 (1-3)†	0 (0-0)	0 (0-0)
	MME	0 (0-0)	3 (2-5)†	4 (3-5)†	7 (5-9)*†	8 (7-9)†	6 (5-8)†	4 (3-6)†	3 (2-5)†	1 (1-4)†	0 (0-1)	0 (0-0)
	MTR	0 (0-0)	5 (2-5)†	5 (3-5)†	8 (6-9)†	9 (7-9)*†	7 (5-7)†	6 (3-6)†	5 (3-5)†	3 (1-4)†	0 (0-1)	0 (0-0)
	MPE	0 (0-0)	3 (2-5)†	5 (3-5)†	9 (6-9)†	9 (7-9)*†	7 (5-7)†	6 (3-6)†	5 (2-5)†	4 (1-4)†	0 (0-1)	0 (0-0)
HR (beats minute⁻¹)	MED	105 ± 7	90 ± 7†	85 ± 7†	81 ± 7†	78 ± 7†	79 ± 8†	79 ± 8†	79 ± 8†	83 ± 8†	87 ± 8†	106 ± 7
	MMO	107 ± 10	92 ± 9†	87 ± 9†	83 ± 9†	80 ± 9†	81 ± 9†	80 ± 9†	81 ± 10†	85 ± 10†	89 ± 9†	107 ± 10
	MME	106 ± 11	91 ± 10†	86 ± 10†	83 ± 9†	80 ± 9†	83 ± 9†	82 ± 10†	83 ± 10†	87 ± 9†	92 ± 9†	105 ± 9
	MTR	105 ± 6	90 ± 5†	84 ± 5†	81 ± 5†	77 ± 5†	80 ± 5†	79 ± 5†	79 ± 4†	83 ± 4†	88 ± 4†	106 ± 6
	MPE	106 ± 11	88 ± 12†	83 ± 12†	78 ± 11†	75 ± 10†	81 ± 10†	79 ± 10†	80 ± 10†	84 ± 9†	90 ± 9†	105 ± 8
RR (breaths minute⁻¹)	MED	27 ± 2	27 ± 2	27 ± 2	27 ± 2	26 ± 2†	25 ± 2†	25 ± 2†	27 ± 2	26 ± 2	27 ± 2	27 ± 3
	MMO	28 ± 2	27 ± 2	27 ± 2	27 ± 2	26 ± 2†	26 ± 2†	26 ± 2†	27 ± 2	27 ± 2	27 ± 2	28 ± 2
	MME	26 ± 3	26 ± 3	26 ± 3	26 ± 2	25 ± 2†	25 ± 3†	25 ± 3†	26 ± 2	26 ± 2	26 ± 2	26 ± 2
	MTR	26 ± 4	26 ± 3	26 ± 3	26 ± 3	25 ± 2†	26 ± 2†	25 ± 2†	26 ± 3	26 ± 2	26 ± 2	26 ± 2
	MPE	26 ± 4	25 ± 3	26 ± 3	26 ± 3	25 ± 2†	25 ± 2†	25 ± 2†	25 ± 2	26 ± 2	26 ± 3	26 ± 3
RT (°C)	MED	39.3 ± 0.2	39.2 ± 0.4	39.2 ± 0.4	39.4 ± 0.2	39.2 ± 0.3	39.4 ± 0.2	39.3 ± 0.2	39.2 ± 0.3	39 ± 0.4	39 ± 0.4	39.3 ± 0.3
	MMO	39.4 ± 0.1	39.2 ± 0.2	39 ± 0.4	39.2 ± 0.2	39.3 ± 0.3	39.3 ± 0.2	39.2 ± 0.2	39.3 ± 0.2	39.2 ± 0.3	39.3 ± 0.2	39.2 ± 0.3
	MME	39.3 ± 0.3	39.3 ± 0.2	39.3 ± 0.3	39 ± 0.3	39.2 ± 0.4	39.3 ± 0.3	39.3 ± 0.3	39.2 ± 0.3	39.2 ± 0.3	39.3 ± 0.3	39.2 ± 0.2
	MTR	39.2 ± 0.3	39.3 ± 0.3	39.3 ± 0.3	39.3 ± 0.2	39.3 ± 0.3	39.4 ± 0.3	39.4 ± 0.3	39.2 ± 0.3	39.2 ± 0.3	39.3 ± 0.3	39.2 ± 0.2
	MPE	39.2 ± 0.3	39.4 ± 0.3	39.4 ± 0.3	39.2 ± 0.2	39.2 ± 0.3	39.3 ± 0.2	39.3 ± 0.3	39.3 ± 0.3	39.3 ± 0.2	39.4 ± 0.2	39.2 ± 0.3
Ruminal motility (contractions minute⁻¹)	MED	2	2	1†	0†	0†	0†	0†	1†	2	2	2
	MMO	2	2	0†	0†	0†	0†	0†	0†	0†	1†	2
	MME	2	2	0†	0†	0†	0†	0†	0†	0†	0†	2
	MTR	2	2	0†	0†	0†	0†	0†	0†	0†	0†	2
	MPE	2	2	0†	0†	0†	0†	0†	0†	0†	1†	2

The degree of sedation was assessed using a numerical rating scale of 0–10, as follows: 0, no sedation; 1, standing, conscious, decrease head and ear movements; 2, standing, mild head drop; 3, standing, moderate head drop; 4, standing, severe head drop, incoordination; 5, standing, severe head drop, severe incoordination; 6, sternal recumbency, head up; 7, sternal recumbency, head down; 8, lateral recumbency, occasional attempts to attain sternal recumbency; 9, lateral recumbency, uncoordinated movements; and 10, lateral recumbency, no movements (Kästner et al., 2003).

Abbreviations: HR, heart rate; RR, respiratory rate; RT, rectal temperature.

*Significantly different from medetomidine treatment at the same time point ($P < 0.05$).

†Significantly different from baseline value within the same treatment ($P < 0.05$).

Medetomidine alone and in combination with opioids cause significant reduction in HR at 5–105 minutes after administration. Treatment with 15 μg kg^{-1} medetomidine resulted in bradycardia lasting 75 minutes in goats (Mohammad et al., 1991). De Carvalho et al. (2016) and Borges et al. (2016) reported to produce bradycardia for 120 minutes after IV administration opioids in combination with 0.1 mg kg^{-1} xylazine and 5 μg kg^{-1} dexmedetomidine in sheep, respectively.

Opioids in combination with medetomidine produced significant reduction in RR at 30–60 minutes after administration. In Habibian et al. (2011), RR was decreased for 75–120 minutes after epidural administration of tramadol (1 mg kg^{-1}) in lambs. De Carvalho et al. (2016) reported to produce bradypnea for 45–90 minutes by 0.1 mg kg^{-1} xylazine in combination with 0.5 mg kg^{-1} morphine (IV) in sheep. Borges et al. (2016) reported to produce bradypnea for 30–60 minutes after IV administration by 5 μg kg^{-1} dexmedetomidine in combination with 0.5 mg kg^{-1} morphine in sheep.

Ruminal motility was decreased in MED at 10–75 minutes. Also, ruminal hypomotility was reported by Mohammad et al. (1991) during 50 minutes after IV administration of 15 μg kg^{-1} medetomidine in goats. Ruminal motility was decreased for about 80 minutes after IV administration of xylazine (0.4 mg kg^{-1}), medetomidine (20 μg kg^{-1}), and dexmedetomidine (5 μg kg^{-1}) in camels (Samimi et al., 2019, 2020). Compared with medetomidine, ruminal motility was significantly lower in MED/opioid treatments at 75–105 minutes after administration in this study. Decrease in gastrointestinal motility following different α_2-adrenergic agonists in combination with opioids has been reported in horses (Boscan et al., 2006). By affecting the μ receptor in CNS and peripheral tissues, opioids reduce intestinal motility (Boscan et al., 2006). Treatment with MED/opioids could predispose unhealthy animals to digestive tract events such as colic and impaction.

In this study, no significant differences were observed in RT and CRT at different time points in each treatment or between treatments in this study. Similarly, RT was unchanged for about 120 minutes after IV administration of dexmedetomidine (5 μg kg^{-1}) in combination with methadone (0.5 mg kg^{-1}), morphine (0.5 mg kg^{-1}) and tramadol (5 mg kg^{-1}) in sheep (Borges et al., 2016). Intravenous administration of 0.1 mg kg^{-1} xylazine in combination with 5 mg kg^{-1} tramadol, 0.5 mg kg^{-1} methadone, and 0.5 mg kg^{-1} morphine was reported to produce on changes in RT in sheep (De Carvalho et al., 2016). Also, no changes in RT were reported by Mohammad et al. (1991) after IV administration of 15 μg kg^{-1} medetomidine in goats.

Different combinations of α_2-adregenrgic agonists and narcotics with different routes of administration such as intramuscular or epidural are recommended. Moreover, it would have been preferable to record measurements slightly longer.

5 | CONCLUSION

Clinical adverse effects were observed up to 90 minutes after IV administration of medetomidine/opioids in goats in this study. The duration of sedation was up to 90 minutes after IV administration

medetomidine (20 μg kg^{-1}) alone and in combination with morphine (0.1 mg kg^{-1}), methadone (0.2 mg kg^{-1}), tramadol (2 mg kg^{-1}), and pethidine (1 mg kg^{-1}) in goats in this study. The use of combinations of medetomidine/opioids would be considered for superior sedation at 15–30 minutes after administration in goats. No significant differences were detected among opioids in combination with medetomidine in goats. More investigations with evaluation of cardiorespiratory effects are recommended.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

ETHICAL APPROVAL

All ethical considerations including utilizing animals were considered cautiously. The trial convention was affirmed by the animal welfare committee (which was covered IACUC approval) of the Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman, Kerman, Iran (institutional approval number: IR.UK.VETMED.REC.1399.023). All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

AUTHOR CONTRIBUTIONS

M. Salarpour: Data curation; funding acquisition; investigation; methodology; visualization; writing–original draft; formal analysis; project administration; E. Sakhaee: Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; validation; visualization; A. S. Samimi: Conceptualization; data curation; formal analysis; project administration; resources; writing–review and editing; software; supervision; visualization; writing–original draft; O. Azari: Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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