DOI: 10.1002/vms3.1023

ORIGINAL ARTICLE

WILEY

Comparing the effects of intravenous injection and intranasal atomisation of detomidine in sheep

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Funding information
Lorestan University, Grant/Award Number: LU-9411511008-21

Abstract

Background: Detomidine is an α-2 agonist sedative drug which reduces the release of norepinephrine in nerves. Administering this drug through intranasal (IN) route could cause direct transmission to the central nervous system. Therefore, IN administration of detomidine would decrease the side effects and the onset of sedation.

Objectives: In this study, IN administration of detomidine in sheep through an atomiser was compared to its IV administration.

Methods: Fifteen mature female sheep with an approximate weight of 49.53 $\pm$ 1.72 kg were used. They were randomly divided into three groups: (1) atomising 10 μg/kg (IND_{10}); (2) IV 10 μg/kg (IVD) and (3) atomising 30 μg/kg (IND_{30}). Following administration, vital signs, electrocardiographic components, sedative score and biochemistry profile were measured after 15, 30 and 60 min, which were compared with the baseline measures.

Results: Bradycardia and the percentage of reduction from the baseline value in the respiratory rate were lower in the IND_{10} group compared to those in the IVD group. There was no significant difference in terms of the temperature and blood oxygen saturation (SpO_2) among all the groups ($p > 0.05$). The level of cortisol declined in all the groups, and in the IND_{30} (60 min), it was significantly different with the baseline value. The level of glucose increased in all the groups compared to the baseline, which was not significant. Insulin concentration was reduced in all the groups, and in the IND_{30} group, it changed significantly 60 min after the drug administration. Sedation onset time was faster in the IV group. However, sedation scores between the two administration methods were not different, and only a dose-dependent increase was found in the sedation score in the atomisation group.

Conclusions: Our findings revealed that IN atomisation of detomidine triggers similar sedation as its IV administration, which could be used as an alternative method.

KEYWORDS
atomiser, cardiopulmonary, detomidine, intravenous, sedation

1 | INTRODUCTION

Sedatives and preanaesthetic drugs are utilised in farm animals for various purposes, including sedation, alleviating the pain generated during surgical procedures, relaxation of muscles, reducing upper airway secretions and saliva and decreasing the dose and complications of anaesthetic drugs (Musk & Wilkes, 2018). Selecting a suitable class of drugs, among the common types, depends on the kind of animal, breed, surgery, health status and accessible instruments. One of the common sedative classes frequently used is α-2 agonist drugs, such as xylazine, medetomidine and detomidine.

Detomidine passes the Blood Brain Barrier (BBB) and spreads all over the brain following an intravenous injection. It reduces the release of norepinephrine in nerves, causes sedation and has tranquilising effects. Other effects are muscle relaxation, analgesic effect, and vomiting in some animals, such as cats (Grove & Ramsay, 2000). It also leads to respiratory weakness, so that the respiratory rate (RR) and tidal volume decrease, followed by which PCO_2 increases. Hence, using this drug, certain special considerations for respiratory function must be applied (Sprayberry & Robinson, 2014). After metabolising, it will be eliminated through urine. Detomidine is used as a sedative and analgesic drug in preanaesthetic period, which is dose-dependent (Plumb, 2008).

Detomidine is frequently administered via intramuscular (IM) or intravenous (IV) routes for sedation or general anaesthesia induction. There are other ways of administration, such as oral and intranasal. Intranasal (IN) administration of detomidine directly transmits it to the brain and spinal cord through olfactory and trigeminal nerves; in this method, it bypasses the Blood Brain Barrier (Sprayberry & Robinson, 2014). Following IV administration of detomidine bradycardia, slight atrial hypoxia, bradypnea, reduction in reticulo-ruminal motility, hyperglycaemia and frequent urination were reported (Kästner, 2006). Following its IN administration, the drug does not enter the systemic blood circulation and its effects on other organs would be limited. IN administration results in the fast onset of the mechanism of action, and the drug is not affected by first-pass metabolism (Grassin-Delyle et al., 2012). Pharmacokinetics of IN detomidine, compared to the IV route, have not been previously studied. However, in a previous paper, pharmacokinetics and bioavailability of IN ketamine were compared to those of IV route and the reported findings revealed a fast and complete IN bioavailability without any significant difference in half-life of the drug between both administration routes (Vlerick et al., 2020). Another study compared intranasal and intramuscular routes of dexmedetomidine in healthy dogs and found that plasma concentrations of the drug in the IN group were lower with the same sedation as in IM dexmedetomidine. Furthermore, IN method does not affect cardiovascular function (Santangelo et al., 2019). This was confirmed by another study, which demonstrated that IN administration of dexmedetomidine triggered less bradycardia compared to the IM route in dogs (Micieli et al., 2017).

Herein, we want to know whether IN administration of detomidine decreases the side effects and increases the speed of drug administration or not. A mucosal atomisation device (MAD nasal) without a needle was used in previous studies for IN administration in dogs (Jafarbeglou & Marjani, 2019). This method of delivery appeared to yield greater bioavailability because of the obtained expanded surface area, allowing a broader distribution across the nasal mucosa while permitting precisely measured doses to be administered (Daley-Yates & Baker, 2001; Henry et al., 1998). This device produces 30–100 μM particles, which are easily and rapidly absorbed. In the present study, IN administration of detomidine was done in sheep with an atomiser device to compare its effects to those of IV administration on clinical signs, some biochemical parameters and electrical activity of heart.

2 | MATERIALS AND METHODS

2.1 | Animals

All the methods and experiments in the current research were approved by the Ethics Committee of Lorestan University (code NO. LU. ECRA.2021.90, Lorestan University, Faculty of Veterinary Medicine, Khorramabad, Iran). This study was carried out in compliance with ARRIVE's guidelines (Percie du Sert et al., 2020). Herein, 15 mature (2.36 $\pm$ 0.39 years old) female Lori sheep with the approximate weight of 49.53 $\pm$ 1.72 kg were used. The animals were obtained from the flock maintained at the educational and research farm of the Faculty of Agriculture and Natural Resources, Lorestan University. The sheep were reared under a semi-intensive farming system; accordingly, they were allowed to graze daily on a natural pasture. The animals were treated for internal and external parasites and vaccinated against PPR. Before being subjected to the study, a pre-experimental physical examination was made on each animal. The sheep were off feed for 18 h prior to the procedure and the water was withheld for 4 h. No deaths or major complications were found during the experiments and no animals were excluded from the study.

2.2 | Procedure and groups

The sheep (n = 15) were randomly divided into three groups, using simple randomisation method, as follows:

- Group 1 (IND_{10}): Intranasal atomising (MAD 300, LMA MAD Nasal™ Devices, Teleflex, Morrisville, NC, USA) of detomidine (Sedator™ Injection, Randlab, Chipping Norton NSW 2170, Australia) with the dose of 10 μg/kg (Grimm et al., 2015) in 1 ml normal saline was performed (n = 5).
- Group 2 (IVD): IV administration of detomidine with the dose of 10 μg/kg (Grimm et al., 2015) in 1 ml normal saline was performed (n = 5).
- Group 3 (IND_{30}): Atomising detomidine with the dose of 30 μg/kg (Grimm et al., 2015) in 1 ml normal saline was done (n = 5).

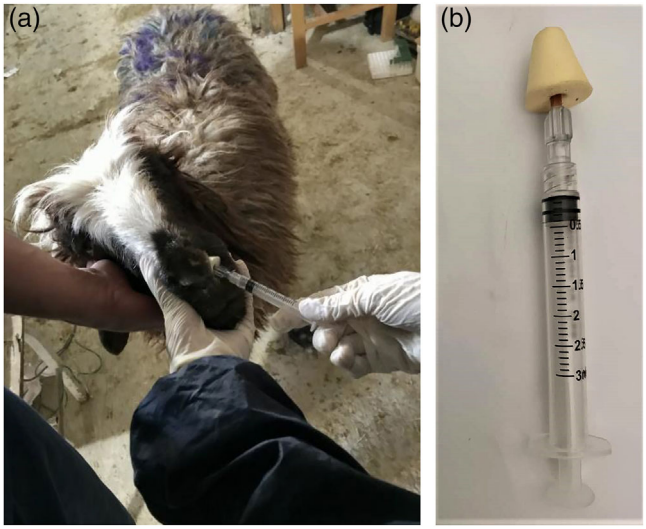

FIGURE 1 (a) Intranasal (IN) administration of detomidine in sheep. (b) MAD intranasal mucosal atomisation device (MAD 300, LMA MAD Nasal™ Devices, Teleflex, Morrisville, NC, USA)

For administration through the atomiser, the sheep were restrained while the head was 30–45° upwards and the atomiser device was inserted along with the nasal septum ventrally. Subsequently, the drug was administered in to the nasal cavity (Figure 1). Based on the manufacturer company, there is 0.1 ml of 'dead space' in the chamber of the MAD; therefore, an additional 0.1 ml of medication was drawn before administration in order to make up for this space. In the IVD group, the jugular groove of the sheep was disinfected with 70% isopropyl alcohol, and the calculated dose of detomidine was slowly injected into the jugular vein via a disposable syringe and 18-G needle. The following parameters were assessed in all the groups prior to the drug administration (0 min), and following 15, 30 and 60 min of the administration: vital signs, ECG evaluation, biochemistry profile and sedation score.

2.3 | Assessment of vital signs

The sheep were restrained in a standard box for 20 min so that the normal vital signs could be obtained. Afterwards, the heart rate, respiratory rate, rectal temperature and SpO_2 were recorded. A standard manual thermometer was inserted into the rectum and allowed to remain there for approximately 2 min to obtain the rectal temperature. Respiration and heart rates were obtained through the use of a stethoscope (250 Premium Lite, Tytan Co., Taiwan). The blood oxygen saturation (SpO_2) was measured with pulse oximetry (Shanghi International holding Corp., GMBH, China) and recorded at each timepoint. SpO_2 sensors were positioned at both ears and measured in duplicate. Pulse oximetry continuously estimates the average saturation of haemoglobin (Hb) with oxygen (SpO_2) in pulsatile arterial blood. The pulse oximeter has two light-emitting diodes (LEDs) emitting red (660 nm) and infrared (range: 905–950 nm) light and a photosensor positioned opposite the LED (transmittance probe). As the light passes through tissues, a certain amount is absorbed and less light is detected. The amount of light absorbed depends on the type of Hb and the wavelength of the light. The LED cycles between diodes occur by switching each of the diodes on and off, which happen several times a second in order to compare the light absorption at different periods of the cardiac cycle, and between the two different light wavelengths.

2.4 | ECG evaluation

Before obtaining the ECG, the animals' health was confirmed with physical examination. At the time of recording ECG, the animals stood up on their limbs without movement. No clipping or shaving was carried out for attachment of the electrodes. A base apex bipolar lead was used for recording. Alligator types of electrodes were utilized for this recording. The related part of skin was not allowed to dry up and were moistened with 70% isopropyl alcohol. The positive electrode (left arm) was positioned in the fifth left intercostal space at the elbow level near the cardiac apex while the negative electrode (right arm) was attached to the left jugular groove at the cardiac base top, and the ground lead was placed further from the heart (Constable et al., 2016). Electrocardiograms were taken for at least 2 min, all of which were obtained on a six-channel electrocardiographic automatic machine (Kenz Cardico 302, Suzuken, Japan) with the paper speed of 25 mm/s and calibration of 10 mm equal to 1 mV. The records were placed in an opaque pack with no water and light exposure. Subsequently, they were scanned and magnified. At this stage, the amplitude (voltage) of P, Q, R, S and T waves in addition to the duration (seconds) of P, QRS, T waves and P-R, Q-T, R-R and PP intervals, as well as PR, ST and TP segments were measured and recorded. Very small waves that were not properly visible were considered immeasurable (almost isoelectric). Twenty consecutive waves, segments and intervals were examined, following which the mean of each component was measured. Heart rate was determined by measuring the R-R interval.

2.5 | Blood collection and biochemical measurement

The glucose, insulin and cortisol concentration were measured. In each time point, after debugging the alligator electrode clamps, 5 ml of blood was collected from the jugular vein in tubes containing a clot activator (LV-12105, Levram Lifesciences Pvt. Ltd., India). They were kept in an ice bag and transported to the laboratory of Veterinary Teaching Hospital (VTH) of Lorestan University. The samples were centrifuged (ROTOFIX 32A, Andreas Hettich GmbH & Co., Tuttlingen, Germany) at 3000 rpm for 15 min and the serum was isolated and transferred into microtubes (2 ml, Green Mall, Jingsu, China). The serum samples were aliquoted and stored at −21°C for further analysis.

Glucose concentration of venous blood samples were immediately determined in a drop of fresh blood from the tip of the needle using an electrochemical point-of-care meter (SMBG GM110, Bionime Co., Taichung city, Taiwan). The basic concept of the glucose biosensor in

this glucometer is based on the fact that the immobilised GOx catalyses the oxidation of β-D-glucose by molecular oxygen producing gluconic acid and hydrogen peroxide. To evaluate repeatability, accuracy, and within-run imprecision of glucometer, one sample was analysed for 15 consecutive times at intervals of 15 s; the CVs were determined and compared with that of the control samples.

Insulin concentrations were determined with commercial kit (Sheep specified, Sandwich ELISA, Cusabio Co., Houston, TX, USA) using ELISA reader (Stat fax 2100, Awareness Technology INC., USA) following the instructions. The sensitivity of the insulin kit is 5 μIU/ml, and the detection range is between 8 and 100 μIU/ml, as reported in the guidelines for use. The precision of the kit, estimated with intra- and inter-assay coefficients of variation (CV), was respectively 5.07% and 6.29% for low and 8.40% and 9.23% for high insulin values in sheep serum.

Cortisol concentration of the serum samples were measured with ELISA kit (Human specified, Competitive, Boster Biological Technology, Pleasanton CA, USA) according to the manufacturer's instructions. The sensitivity of the cortisol kit is 1 nmol/dl, and the assay range is between 1 and 10 nmol/dl, as reported in the guidelines for use. The precision of the kit was estimated with intra- and inter-assay CVs, which were respectively 5.23% and 6.78% for low and 7.33% and 8.55% for high cortisol values in sheep serum.

2.6 | Sedation score and onset

The time of sedation onset was recorded right after the drug administration. Additionally, sedation was assessed through observing the animals without further stimulation, always by the same person who was blind to the experiments and groups. The observed behaviour was assigned a score of 0 to 10, which is as follows: 0 as standing, alert, normal behaviour; 1 as standing, alert, reduced head and ear movements; 2 as standing, slight head drop; 3 as standing, moderate head drop; 4 as standing, severe head drop + ataxia; 5 as standing, severe head drop + severe ataxia (stumbling); 6 as sternal recumbency, head up; 7 as sternal recumbency, unable to support the head; 8 as lateral recumbency, occasional attempts to obtain sternal recumbency; 9 as lateral recumbency, uncoordinated head and leg movements; 10 as lateral recumbency, no movements (Kästner et al., 2003).

2.7 | Statistical analysis

Data were tested for normality using the Kolmogorov–Smirnov normality test. The vital signs, biochemical parameters, and electrocardiographic components were compared to the baseline values (T_0) utilising repeated measures analysis of variance, followed by Duncan's post hoc test for comparing the treatments. The statistical model was designed and Mauchly's test of sphericity was performed. If the epsilon static of Mauchly's test of sphericity was over 0.05, the sphericity hypothesis would be rejected and ANOVA test was performed after Greenhouse–Geisser and Huynh–Feldt tests. The treatments were compared concerning the times to onset and duration of sedation score using a paired samples *t*-test. A one-way repeated measure ANOVA followed by Bonferroni's test was used for comparing the onset and duration of sedation score between the treatments. Statistical analysis was performed using MedCalc (Ver. 14.8.1, Ostend, Belgium) and Analyse-it software packages for Windows (Ver. 4.80.8, Leeds, UK). The $p < 0.05$ was considered to be statistically significant. The data are shown as mean ± standard deviation (SD).

3 | RESULTS

3.1 | Vital signs

3.1.1 | Heart rate (HR)

Table 1 represents the results related to this part. In the IND_{10} group, no significant difference was observed between the baseline value and the other measured values ($p > 0.05$). However, in the IVD group, after 15 min, HR significantly declined compared to that of the baseline ($p < 0.05$). In the IND_{30} group, the heart rate significantly decreased compared to the baseline value 15 and 30 min after drug administration ($p < 0.05$). A 16% drop from the baseline value was observed in the IND_{10} group 30 min after drug administration. A drop of 25% from the baseline value was seen in the IVD group 15 min following the injection and a 28% decrease was found in the IND_{30} group 15 and 30 min after detomidine administration.

3.1.2 | Respiratory rate (RR)

Based on Table 1, no significant differences were observed among the baseline values and the other measured values at IND_{10} and IVD groups ($p > 0.05$). In the IND_{30} group, RR was remarkably reduced from the baseline 30 and 60 min after detomidine atomisation ($p < 0.05$). In the IND_{10} group, a maximum drop of 27% from the baseline and in the IVD group, a maximum drop of 37% from the baseline were found. The maximum drop from the baseline was 41% in the IND_{30} group, 60 min following the drug administration.

3.1.3 | Temperature

The results indicated no significant differences among the groups ($p > 0.05$) (Table 1).

3.1.4 | SpO_2

According to Table 1, in the IND_{10} and IVD groups, SpO_2 increased 15 and 60 min after drug administration, which was not significant compared to the baseline value ($p > 0.05$). In the IND_{30} group, SpO_2 in all the measured times was elevated compared to the baseline, which was not significant ($p > 0.05$). Increments of 11% and 8% from the baseline

TABLE 1 Vital signs in different experimental groups of the study

Variable	Group	0 Min	15 Min	30 Min	60 Min
HR (beats/min)	IND 10	60.00 ± 7.35	58.00 ± 12.49	50.40 ± 9.10	54.00 ± 8.48
	IVD	51.60 ± 6.84	38.40 ± 3.29*#	39.60 ± 5.37*	44.40 ± 6.84
	IND 30	46.80 ± 5.02	33.60 ± 5.37*#	33.60 ± 5.37*#	37.20 ± 2.68*
RR (breathes/min)	IND 10	34.00 ± 9.38	24.50 ± 1.00 [b]	34.00 ± 5.29 [a]	32.50 ± 7.55[a]
	IVD	38.80 ± 8.67	26.00 ± 9.90	24.40 ± 8.05	25.60 ± 6.07
	IND 30	31.20 ± 2.28	21.60 ± 7.13	21.60 ± 5.18*#	18.40 ± 5.37*#
Temperature (°C)	IND 10	39.340 ± 0.30	39.57 ± 0.29	39.66 ± 0.44	39.94 ± 0.39
	IVD	39.26 ± 0.36	39.18 ± 0.22	39.38 ± 0.62	39.10 ± 0.29
	IND 30	39.06 ± 0.39	39.16 ± 0.15	38.90 ± 0.68	39.06 ± 0.72
SpO_2 (%)	IND 10	80.48 ± 5.72	89.75 ± 9.32	81.00 ± 10.86	89.25 ± 5.05
	IVD	79.60 ± 10.67	86.00 ± 4.90	82.80 ± 5.80	86.00 ± 9.45
	IND 30	72.20 ± 17.14	77.00 ± 12.55	84.20 ± 6.02	81.00 ± 9.54

Note. The uneven letters show the significant difference in each group.
HR: heart rate, RR: respiratory rate, SpO_2: saturation oxygen pressure.
*Significant difference to group IND 10.
#Significant difference with baseline values ($p < 0.05$).

value were found in the IND_{10} and IVD groups 15 and 60 min following the detomidine administration. The maximum elevation of SpO_2 from the baseline in the IND_{30} group was 16%, 30 min after the detomidine atomisation (Table 1).

3.1.5 | ECG

According to Tables 2 and 3, there were no significant differences among the baseline values and the measured ones concerning ECG intervals and ECG segments ($p > 0.05$). The ECG assessment revealed significant differences in various factors between the groups. Concerning the intervals at 15 min after the administration, the P-R of the IVD group was significantly lower than that of the IND_{30} group ($p < 0.05$), and the R-R factor in the IND 10 group was significantly lower than that of the IND 30 group. There was no significant difference between the groups in terms of P-P and Q-T intervals duration at this time-point ($p > 0.05$) (Table 2). Only P-P interval duration of the IVD group was significantly lower than that of the IND_{30} group 30 min after the administration ($p < 0.05$). All parameters of the IND_{30} group were significantly higher compared to those of the IND_{10} and IVD groups 60 min following the administration, except for the P-P interval duration, concerning which only the IND_{30} group was significantly different with the IND_{10} group ($p < 0.05$).

Regarding segments, 15 min after the administration, the IVD group was significantly higher than the IND_{10} group in terms of PR, ST and TP ECG segments ($p < 0.05$). Moreover, the IND_{30} group had significantly lower PR and TP duration in comparison with the IVD and IND_{10} groups, respectively ($p < 0.05$). The results were similar 30 min after the administration, except that there was no significant difference in TP segment duration between the IVD and IND_{30} groups. Sixty minutes following the administration, only the IVD group was significantly higher than the IND_{10} and IND_{30} groups in terms of PR and ST segments, respectively ($p < 0.05$).

Regarding cardiac arrhythmia and conduction disturbances, the study revealed different types of electrocardiographic abnormalities, such as sinus bradycardia, sinus tachycardia, sinus arrhythmia, wandering peacemaker and electrical alternances (Figure 2). The frequency of cardiac dysrhythmias in the IND_{10} group was significantly lower than that in the other treatments and P-R interval was stable. Meanwhile, the frequency of sinus bradycardia and wandering peacemaker in the IVD group was higher than that in the other groups.

3.2 | Biochemical parameters

3.2.1 | Glucose

According to the results, no significant differences were observed among the baseline values and the other measured values for the glucose concentration ($p > 0.05$) (Table 3). The maximum increment in the glucose level was 54% in the IND_{10} group 60 min following the detomidine atomisation. In the IVD group, a 29% elevation from the baseline was observed, 15 min after the drug injection. The glucose level increased (31%) 30 and 60 min after the drug administration.

3.2.2 | Cortisol

Cortisol levels are depicted in Table 3. The concentration of cortisol at all the time points declined in comparison to that of the baselines; however, this reduction was only significant in the IND_{30} group 60 min after the drug administration ($p < 0.05$). The maximum decrement of cortisol

TABLE 2 Duration (seconds) of ECG intervals and segments and amplitude (mV) of waves in different experimental groups of the study

	Variable	Group	0 Min	15 Min	30 Min	60 Min
Intervals	P-P (S)	IND_{10}	0.591 ± 0.059	0.654 ± 0.146	0.719 ± 0.173	0.730 ± 0.124
		IVD	0.779 ± 0.074	0.902 ± 0.218	0.952 ± 0.114	0.838 ± 0.112
		IND_{30}	0.746 ± 0.058	0.932 ± 0.473	0.977 ± 0.124	0.962 ± 0.077*
	P-R (S)	IND_{10}	0.139 ± 0.035	0.180 ± 0.127	0.324 ± 0.289	0.154 ± 0.016†
		IVD	0.139 ± 0.017	0.130 ± 0.017†	0.138 ± 0.012†	0.130 ± 0.008*†
		IND_{30}	0.150 ± 0.035	0.310 ± 0.115	0.221 ± 0.046	0.232 ± 0.068
	Q-T (S)	IND_{10}	0.308 ± 0.031	0.330 ± 0.057	0.334 ± 0.047	0.372 ± 0.039†
		IVD	0.334 ± 0.033	0.348 ± 0.041	0.367 ± 0.024	0.368 ± 0.026†
	R-R (S)	IND_{30}	0.390 ± 0.038	0.457 ± 0.137	0.437 ± 0.077	0.520 ± 0.052
		IND_{10}	0.599 ± 0.079	0.636 ± 0.131†	0.727 ± 0.181	0.709 ± 0.116†
		IVD	0.754 ± 0.056	0.906 ± 0.178	0.946 ± 0.111	0.818 ± 0.095†
		IND_{30}	0.754 ± 0.054	1.094 ± 0.133	1.072 ± 0.128	0.990 ± 0.066
Segments	PR (S)	IND_{10}	0.049 ± 0.007	0.042 ± 0.001[a]	0.050 ± 0.005[b]	0.049 ± 0.011[b]
		IVD	0.082 ± 0.007	0.080 ± 0.010*†	0.080 ± 0.009*†	0.077 ± 0.017*†
		IND_{30}	0.046 ± 0.016	0.049 ± 0.009	0.048 ± 0.013	0.046 ± 0.015
	ST (S)	IND_{10}	0.106 ± 0.072	0.133 ± 0.041+	0.138 ± 0.054+	0.143 ± 0.047+
		IVD	0.246 ± 0.032	0.260 ± 0.043	0.276 ± 0.019	0.274 ± 0.042
		IND_{30}	0.359 ± 0.383	0.161 ± 0.047	0.214 ± 0.069	0.192 ± 0.115
	TP (S)	IND_{10}	0.156 ± 0.071	0.139 ± 0.060+†[a]	0.207 ± 0.056[b]+	0.217 ± 0.093[b]
		IVD	0.312 ± 0.048	0.446 ± 0.182	0.465 ± 0.124	0.352 ± 0.093
		IND_{30}	0.211 ± 0.048	0.377 ± 0.108	0.356 ± 0.163	0.380 ± 0.125
Waves	Q (mV)	IND_{10}	0.02 ± 0.03	0.07 ± 0.12[a]	0.05 ± 0.10[a]	0.01 ± 0.02[b]
		IVD	0.004 ± 0.002	0.015 ± 0.007[a]*†	0.003 ± 0.001[b]*†	0.002 ± 0.001[c]*†
		IND_{30}	0.02 ± 0.02	0.01 ± 0.03[a]*	0.008 ± 0.02[b]*	0.01 ± 0.03[a]
	T (mV)	IND_{10}	0.41 ± 0.22	0.30 ± 0.07	0.26 ± 0.10	0.30 ± 0.05
		IVD	0.13 ± 0.09	0.20 ± 0.04*	0.21 ± 0.04	0.20 ± 0.07*
		IND_{30}	0.24 ± 0.08	0.28 ± 0.06	0.20 ± 0.04	0.20 ± 0.05*

Note. Data presented as mean ± SD. The dissimilar letters show the significant difference within group.
*,+,† The significant difference to the group IND_{10}, IVD and IND_{30}, respectively.

TABLE 3 Biochemistry profile in different experimental groups of the study

Variable	Group	0 Min	15 Min	30 Min	60 Min
Glucose (mg/dl)	IND_{10}	70.80 ± 14.99	85.80 ± 20.25	93.25 ± 29.59	108.20 ± 26.82
	IVD	93.00 ± 17.89	120.00 ± 76.40	99.80 ± 14.02	116.40 ± 14.36
	IND_{30}	91.00 ± 8.25	114.00 ± 22.84	120.40 ± 38.85	120.60 ± 38.93
Cortisol (nmol/dl)	IND_{10}	6.44 ± 0.49	6.31 ± 0.37	5.92 ± 0.44	5.63 ± 0.35
	IVD	6.07 ± 0.56	5.45 ± 0.24*†	5.44 ± 0.25	5.72 ± 0.13
	IND_{30}	6.41 ± 0.67	6.40 ± 0.60[a]	5.82 ± 0.52[a]	5.28 ± 0.41[b#]
Insulin (μIU/ml)	IND_{10}	13.59 ± 1.69	13.54 ± 1.76	13.34 ± 1.70	13.14 ± 1.70
	IVD	11.51 ± 2.17	10.79 ± 1.99	10.54 ± 2.05	10.36 ± 2.07
	IND_{30}	11.74 ± 1.52	11.66 ± 1.42	10.26 ± 1.21*	9.25 ± 0.82*#

Note. The dissimilar letters show the significant difference within group.
*,+,† The significant difference to the group IND_{10} and IVD and IND_{30}, respectively.
Significant difference with baseline values ($p < 0.05$).

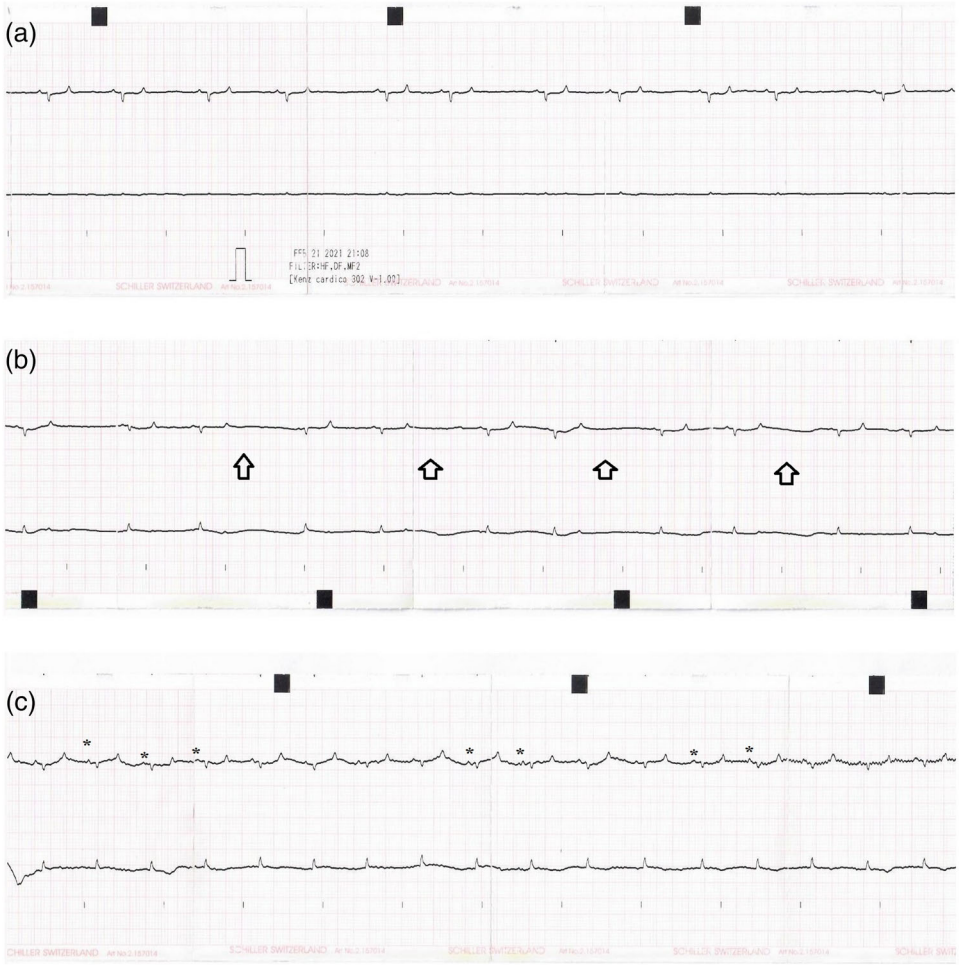

FIGURE 2 (a) An electrocardiogram recorded from a sheep of IVD group (case No. 2) at 15 min after detomidine administration (HR: 60 beats per min) with sinus bradycardia. (b) An electrocardiogram recorded from a sheep of IN_{30} group (case No. 5) at 30 min after detomidine administration (HR: 60 beats per min) with sinus arrhythmia. (c) An electrocardiogram recorded from a sheep of IN_{10} group (Case No. 5) at 60 min after detomidine administration (HR: 90 beats per min) with wandering peacemaker (Base-apex lead electrocardiography; 25 mm/s; 10 mm/mV)

value from the baseline was 12%, 10% and 17% in the IND_{10}, IVD and IND_{30} groups, respectively.

3.2.3 | Insulin

Insulin levels are also shown in Table 3. Based on the table, insulin decreased from baseline at all time points and it was significant only 60 min after atomisation in the IND_{30} group. In the IND_{10} group, an approximately 4% drop was observed compared to the baseline 60 min after the administration. A 9% drop was found in the level of insulin compared to the baseline value in the IVD group 60 min after the administration. This amount was 21% in the IND_{30} group (Table 3).

3.3 | Sedation onset time

According to the results, the mean sedation onset time for groups IND_{10}, IVD and IND_{30} was 10, 5 and 8 min, respectively, where there was only a significant difference between the IND_{10} and IVD groups ($p < 0.05$) (Table 4).

TABLE 4 Sedation onset time in different experimental groups of the study

Variable	Group	Minimum	Median	Maximum
Onset	IND_{10}	6.00	10.00	12.00
	IVD	2.00*	5.00*	9.00*
	IND_{30}	7.00	8.00	11.00

*Significant difference to the group IND_{10}.

3.4 | Sedation score

The groups were different concerning sedation score. In the IVD group, the highest sedation score (2.60 ± 0.89) among evaluated intervals was at 15 min after the drug injection, after which a decline in the scores

TABLE 5 Sedation score in different experimental groups of the study

Variable	Group	0 Min	15 Min	30 Min	60 Min
Score*	IND_{10}	0	1.40 ± 1.14	$2.00 \pm 1.00^{\dagger}$	$1.20 \pm 0.84^{\dagger}$
	IVD	0	2.60 ± 0.89	$2.40 \pm 1.14^{\dagger}$	$2.20 \pm 1.79^{\dagger}$
	IND_{30}	0	2.60 ± 1.34^{a}	4.60 ± 0.89^{b}	4.00 ± 0.00^{b}

Note. The dissimilar letters show the significant difference within group.
†The significant difference with the group IND_{30}.
*Sedation score evaluated based on Kästner et al. (2003).

was observed. Nonetheless, the IND_{10} and IND_{30} groups showed the peak sedation 30 min following the administration. The sedation in the IND_{30} group was significantly higher than that in the IND_{10} and IVD groups 30 and 60 min after the administration ($p < 0.05$) (Table 5).

4 | DISCUSSION

Intranasal atomiser administration is a noninvasive route, suitable for drug delivery, especially for anaesthetic purposes. That is because the nose has numerous vessels through which drug can be absorbed and transmitted to the brain quickly (Pardeshi & Belgamwar, 2013). Atomisers break the drug into 30–100 μm drops and increase the absorbance surface effectively (Musulin et al., 2011).

All α-2 adrenergic agonists can cause bradycardia (Duncan et al., 2018). Previous studies demonstrated that bradycardia is caused by detomidine with the dose of 30 μg/kg in sheep (Celly et al., 1997) and 10 μg/kg in cows (Ribeiro et al., 2012). Additionally, Khan et al. (2004) reported bradycardia and hypotension after detomidine and xylazine administration in small ruminants (Khan et al., 2004). Jafarbeglou and Marjani (2019) compared the anaesthetic effect of medetomidine in different routes, including an atomiser, nasal drop and intramuscular (IM) in dogs. Despite some differences between these groups, they were not statistically significant (Jafarbeglou & Marjani, 2019). In agreement with previous studies, in the present research, the animals' heart rate decreased in all studied groups. The HR reductions in the IVD and IND_{30} groups were significant compared to that in the baseline, and in the IND_{10} group, the alterations were not significant. Bradycardia, which has been also shown in previous studies, may be due to blocking the sympathetic nerve by reabsorbing the presynaptic norepinephrine and stimulating the vagal nerve and the parasympathetic nerve impulses (Hsu & Hummel, 1981).

In the present study, after detomidine treatment, a decreased respiratory rate was detected compared to the time before drug injection. These are in line with the studies by Khan et al. (2004) and Aghajanian and Rogawski (1983). Malhi et al. (2015) compared the effects of xylazine, detomidine and medetomidine on heart rate, respiratory rate and glucose blood concentration in sheep. They found that the respiratory rate in both xylazine and medetomidine groups was significantly lower than that in the detomidine group ($p < 0.05$), which is in complete agreement with our findings (Malhi et al., 2015).

De Moura et al. (2018) investigated the sedative effect of 20 μg/kg bolus of intravenous detomidine followed by continuous administration of 60 μg/kg/h in Santa Ines sheep. Their results revealed a gradual decline in the temperature, and after 45 min, the sheep experienced the lowest temperature (De Moura et al., 2018). In contrast to Moura et al. (2018), in the present study, no significant difference was observed in the rectal temperature of Lori breed sheep. The authors hypothesise that this could be due to the breed, dose and environmental differences.

Previous research showed that IV administration of α-2 adrenergic agonists causes hypoxaemia in sheep (Buerkle & Yaksh, 1998; Kästner et al., 2005). Herein, no significant differences were found in the SpO_2 percentage, as a result of which hypoxaemia was not confirmed.

Samimi and Azeri (2017) administered 50 μg/kg of detomidine via IV route and evaluated the clinical signs, blood electrolytes, ECG parameters and heart arrhythmia on *Camelus dromedaries*. They found that P, QRS and T waves did not change significantly during the anaesthesia although there were significantly longer R-R and Q-T intervals. In the present paper, these waves did not indicate any significant changes among the samples in one group, but there was a significant difference between the groups, in which T and R waves had a significantly higher wavelength in atomiser groups than in IV group. Moreover, R-R and Q-T intervals revealed a significantly longer time. In both studies, there was no remarkable difference in P-P interval, which finally resulted in arrhythmia (Samimi & Azari, 2017). The duration of ECG waves, like their amplitude, may also be influenced by physiological and pathological factors. Certain researchers believe that due to considerable variability in T wave amplitude in healthy animals, it cannot be used as an indicator for assessment of animals' health (Edwards, 1993). Various factors can cause arrhythmia, including myocardial disease, autonomic nervous system problem and acid-base imbalance. In our study, we did not find any pathologic arrhythmia and only physiologic arrhythmias were detected. Surprisingly, there was no electrolyte concentration problems or acid-base imbalance in the study conducted by Samimi and Azeri, which may be on account of the detomidine effect on the autonomic system, causing sinoatrial node blocking and vagal reflex (Alexander & Irvine, 2000; Plumb, 2008).

In a study conducted by Malhi et al. (2015) on the effects of xylazine, detomidine and medetomidine on blood glucose level in sheep, a significant rise was observed in the amount of blood glucose following the administration of these drugs (Malhi et al., 2015). Another study by Brockman investigated the effects of xylazine on plasma glucose, glucagon, and insulin concentrations in sheep, whose results revealed hyperglycaemia and that the levels of insulin were reduced 30 min after the drug administration (Brockman, 1981). The probable

mechanism by which xylazine triggers hyperglycaemia and hyperinsulinaemia in cattle is mediated by α2-adrenergic receptors, possibly in β-cells of pancreatic islets which inhibit the release of insulin (Hsu & Hummel, 1981). In agreement with previous studies, in the present work, the level of blood glucose increased and insulin concentration was reduced in all studied groups. Moreover, the maximum increment in the glucose level was 54%, 29% and 31% in the IND_{10}, IVD and IND_{30} groups, respectively. The maximum reduction in the insulin level was 4%, 9% and 21% in the IND_{10}, IVD and IND_{30} groups, respectively. Hence, glucose further increased in the IND_{10} group compared with the other groups with the minimum reduction in the insulin level.

In the study by Aghamiri et al. (2022), the effects of xylazine, detomidine, medetomidine and dexmedetomidine were investigated during laparoscopic SCNT embryo transfer on pregnancy rate and some physiological variables in goats. Their findings revealed that serum cortisol concentration significantly decreased in the α2-adrenergic agonists groups at the time points of 45 and 60 min (Aghamiri et al., 2022). In another paper, the level of cortisol in a detomidine-administered cattle was evaluated, where the authors found that in all groups, the level of plasma cortisol declined (Gnanasekar et al., 2019). In line with previous studies, herein, a 12%, 10% and 17% reduction from the baseline in the cortisol levels was observed in the IND_{10}, IVD and IND_{30} groups, respectively.

Kästner et al. (2003), in a study evaluating pharmacokinetics and sedative effects of intramuscular medetomidine in sheep, reported peak sedation 30–40 min following medetomidine administration. In agreement with previous findings, in the present study, the peak sedation score was observed 30 min following detomidine administration in experimental groups.

5 | CONCLUSION

Bradycardia was lower in the IND_{10} group compared to that in the IVD group and no significant difference was observed for the respiratory rate in the IND_{10} group compared to that in the IVD group. Due to the cortisol drops in comparison with the baseline level, it can be interpreted that lower stress occurred in the atomisation group. The sedation onset time was faster in the IV group. However, the sedation score between the two administration routes were not different and only a dose-dependent increase in the sedation score was found in the atomisation group. Overall, it could be concluded that the application of 10 μg/kg detomidine via intranasal is similar to intravenous injection with similar few side effects, and that intranasal route could be suggested as an alternative for the intravenous route. There are some limitations in the present study for study design and data collection and intervals for monitoring vital signs and sedation are wide. More studies with lower time intervals are required to exactly understand the IN-administration effects.

AUTHOR CONTRIBUTIONS

Touran Tahmasbi: conceptualisation, methodology, investigation, writing – original draft. Abbas Raisi: project administration, conceptualisation, methodology, investigation, writing – review & editing. Amir Zakian: visualisation, resources, data curation, formal analysis. Majid Khaldari: validation, software, writing – review & editing, supervision.

ACKNOWLEDGEMENTS

This study was extracted from the DVM thesis of Touran Tahmasbi performed in the Lorestan University. The authors would like to thank the vice chancellor of research of Lorestan University and Dr. Ali Kakanezhadi for his help.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All the methods and experiments in the current research were approved by the Ethics Committee of Lorestan University (code NO. LU. ECRA.2021.90, Lorestan University, Faculty of Veterinary Medicine). This study was carried out in compliance with ARRIVE's guidelines (Grimm et al., 2015).

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PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.1023.

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How to cite this article: Tahmasbi, T., Raisi, A., Zakian, A., & Khaldari, M. (2023). Comparing the effects of intravenous injection and intranasal atomisation of detomidine in sheep. *Veterinary Medicine and Science*, *9*, 353–362. https://doi.org/10.1002/vms3.1023