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Clinicophysiological studies of atropine-tiletamine-zolazepam-sevoflurane anaesthesia with or without dexmedetomidine and butorphanol premedication in dogs

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ABSTRACT

The present study was conducted on twelve clinical patients irrespective of age, breed and sex, randomly divided into two groups, viz., groups A and B consisting of six animals in each. Animals in group A were premedicated with atropine sulphate at the dose rate of 0.04 mg/kg body weight subcutaneously, while in group B, atropine sulphate at the dose rate of 0.04 mg/kg body weight was administered subcutaneously, followed by dexmedetomidine at the dose rate of 5 µg/kg body weight intravenously at a 5 minute interval, followed by butorphanol at the dose rate of 0.1 mg/kg body weight intravenously at a 10 minute interval. Tiletamine-zolazepam was administered intravenously as the induction agent until it took effect and maintenance was conducted with sevoflurane in both groups of animals. Clinicophysiological, haemodynamic and biochemical parameters were evaluated at various time intervals in both groups of animals. Induction time was significantly ($P<0.01$) lower whereas the duration of anaesthesia, sternal recumbency time, standing time, recovery time and complete recovery time were significantly ($P<0.01$) higher in the animals in group B as compared to group A. Excellent quality of muscle relaxation and analgesia was observed in the animals in group B. The abolition of pedal reflex and palpebral reflex was better in the animals in group B as compared to group A. Physiological parameters fluctuated within the normal limits. A significant ($P<0.05$) decrease in PR interval and a significant ($P<0.05$) increase in QRS interval were recorded in the animals in group A. A significant ($P<0.05$) increase in serum glucose and a non-significant ($P>0.05$) decrease in serum albumin, serum total protein, serum urea nitrogen and serum creatinine were recorded in both groups of animals. Thus, it was concluded that the anaesthetic combination of atropine-dexmedetomidine-butorphanol-tiletamine-zolazepam-sevoflurane produces better balanced anaesthesia compared to atropine-tiletamine-zolazepam-sevoflurane anaesthesia in clinical patients during routine surgeries.

Key words: anaesthesia; tiletamine-zolazepam; dexmedetomidine, butorphanol; sevoflurane; canine

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Introduction

The aim of premedication is to induce sedation, provide adequate analgesia, reduce salivation and airway secretion, decrease the potential adverse effects of anaesthetic drugs, and provide adequate induction and a smooth recovery from general anaesthesia. It also offers a wide margin of safety and several pharmacological advantages. Therefore, a suitable combination of drugs is needed to produce a state of balanced anaesthesia in small animal practice. Atropine sulphate is an anticholinergic agent, non-selective muscarinic antagonist, prevents bradycardia, and decreases airway and salivary secretions (LERCHE, 2015). Dexmedetomidine**,** an imidazole compound and alpha-2 adrenergic agonist with very high selectivity for α-2 receptors, produces rapid onset of sedation, analgesia, bradycardia and transient hypertension in the early stage (KUKANICH and PAPICH, 2017; DEGROOT et al., 2020). Butorphanol is a synthetic agonist-antagonist compound with analgesic effect binding with κ receptors. It is a commonly used analgesic for small animals which provides mild sedation, and a limited and short duration of analgesia for less painful procedures (NAM et al., 2013). Tiletamine is an arylcyclohexylamine, structurally related to phencyclidine and ketamine. It is a potent ligand at the PCP binding site of the NMDA receptor, and is pharmacologically classified as a non-competitive NMDA receptor antagonist that induces dissociative anaesthesia (SAHA et al., 2007). Use of tiletamine alone can cause a cataleptic state and convulsion. Thus, it is usually combined with the tranquilizer and anticonvulsant, zolazepam (FERRARI et al., 2005). Zolazepam is a benzodiazepine tranquilizer, similar to diazepam, which acts as a positive allosteric modulator of the gamma aminobutyric acid (GABA) receptor (WALZER and HUBER, 2002). Tiletamine-zolazepam has been used alone or in combination with other anaesthetics drugs in small animals (KRIMINS et al., 2012). Sevoflurane, an ether inhala- tion general anaesthetic produces dose-dependent depression in the cardiovascular, respiratory and central nervous system, with minimal changes in haematobiochemical parameters in small animals (JADON et al., 2008). The present study aimed to evaluate the clinicophysiological, haemodynamic and biochemical effects of two anaesthetic protocols in canine patients.

Materials and methods

The study was carried out in 12 clinical patients irrespective of sex, aged 1.5 to 8.0 years, and weighing 15 to 40 kg, that were presented for minor and major surgical procedures such as cas- tration, ovariohysterectomy, laparotomy, cystoto- my, resection of a canine mammary tumour, aural haematoma and fracture repair, at Dr. I. P. Singh Veterinary Clinical Complex and Trauma Centre, Pantnagar. All the dogs were kept off feed for 12 hours and water was withheld for 6 hours prior to the anaesthesia. The dogs were randomly divided into two groups with six animals in each group. Animals in groups A and B were premedicated with atropine sulphate (0.04 mg/kg b. wt. *s.c.*). An intravenous canula was secured in the cephal- ic vein of the animal and normal saline solution was administered intravenously at the dose rate of 10 mL/kg/h. Five minutes later, dexmedetomidine (5 µg/kg b.wt. *i.v.*) was administered, followed by butorphanol (0.1 mg/kg b. wt. *i.v.*) in group B. Ten minutes after the administration of preanaesthet- ic drugs, animals in both the groups were induced with tiletamine-zolazepam (given intravenously until effect), followed by endotracheal intubation. Anaesthesia was maintained with sevoflurane at an inspired concentration of 2.2% delivered in 100% oxygen. Changes in various clinicophysiological parameters (induction time, duration of anaesthesia, muscle relaxation, palpebral reflex, pedal reflex, analgesia, recovery time, sternal recumbency time, standing time, complete recovery time, required dose of induction agents) were recorded for both the groups. Muscle relaxation was judged in relation to the musculature of abdomen, legs and jaws at various time intervals, by judging the ease with which the jaws could be opened, the limbs could be flexed without much resistance, and the flaccidity of abdominal muscles. It was recorded on a score scale of 1 to 4 (Table 1) (BISHT et al., 2016). Palpebral reflex was recorded as a meas- ure of the depth of sedation by observing the blink of eyelids on touching the medial canthus with an

index finger, and graded on a 0 to 3 score scale at various time intervals (Table 1). Pedal reflex was recorded by observing the flexion or withdrawal of the limb in response to vigorous squeezing and pinching of digits or pads, and graded on 0 to 3 score scale at various time intervals (Table 1) (KUMAR et al., 2014). Analgesia was recorded by observing the response to pin pricks on the body and digits or pads, and graded on 0 to 3 score scale at various time intervals (Table 1) (KINJAVDEKAR et al., 2007). All the reflexes were recorded at 0 (baseline), 5 minutes after premedication, at 5, 10, 15, 20, 30, 45, 60, 75 and 90 minutes after induction with tiletamine-zolazepam. The total dose of tiletamine-zolazepam (mg/kg b.wt.) was calculated in each group. Heart rate, respiration rate, rectal temperature, systolic arterial pressure, diastolic arterial pressure and mean arterial pressure were recorded by veterinary patient monitor (model no. MMED 8000-CV, Beijing Choice Electronic Technology Co. Ltd., Beijing, China) at 0 (baseline), 5 minutes after premedication, at 5, 15, 30, 45, 60, 75, 90 and 180 minutes after induction with tiletamine-zolazepam. Electrocardiography was recorded by a veterinary ECG machine (model Cardivet, Mediglo systems Chandigarh, India) using Lead II at 0 (baseline), 5 minutes after premedication, 5 minutes post-induction and 5 minutes after maintenance with sevoflurane anaesthesia. Biochemical parameters were estimated by a semi-automatic biochemical analyser at 0 (baseline), 30 minutes, 1 hour, 6 hours and 24 hours after baseline value.

The mean and standard error of the clinico-physiological, haemodynamic and biochemical parameters recorded at different time intervals were calculated and analysed between the groups and within each group by the student “t” test and one-way ANOVA using the statistical package SPSS software. The Kruskal Wallis one-way test was used to compare the medians of non-paramet- ric data within the groups at corresponding time intervals. $P<0.05$ and $P<0.01$ were set as the lev- els of significance.

Table 1. Scoring criteria for palpebral reflex, pedal reflex, muscle relaxation and analgesia

Criteria	Score	Observation
Palpebral reflex	0	Intact and strong (quick blink)
	1	Intact but weak (slow response)
	2	Very weak (very slow and occasional)
	3	Abolished
Pedal reflex	0	Intact and strong (strong withdrawal)
	1	Intact but weak (animal responding slowly)
	2	Intact but very light (slow and occasional response)
	3	Abolished completely
Muscle relaxation	1	Tightly closed jaws, stiff limbs resisting all attempts to flex and tight abdominal muscles (No muscle relaxation).
	2	Moderate resistance to opening of the jaws and flexing of the limbs, mild flaccidity of the abdominal muscles (Mild relaxation).
	3	Mild resistance to opening of the jaws and flexing of the limbs, moderate flaccidity of the abdominal muscles (Moderate relaxation).
	4	No resistance to opening of the jaws and flexing of the limbs, completely flaccid abdominal muscles (Excellent relaxation).
Analgesia	0	Strong reaction to pin pricks (No analgesia).
	1	Weak response to pin pricks (Mild analgesia).
	2	Occasional response to pin pricks (Moderate analgesia).
	3	No response to pin pricks (Excellent analgesia).

Results

Clinicophysiological Parameters. The induction time was 81.00±4.34 seconds and 34.83±2.24 seconds in animals in groups A and B, respectively. Induction time was significantly (P<0.01) lower in the animals in group B premedicated with atropine sulphate, dexmedetomidine and butorphanol as compared to group A, who were premedicated with atropine sulphate alone. The duration of anaesthesia, recovery time, sternal recumbency time, standing time and complete recovery time were 66.50±3.45 minutes, 6.17±0.31 minutes, 11.00±0.68 minutes, 16.67±1.38 minutes and 29.50±1.84 minutes, respectively, in group A and 105.17±2.16 minutes, 9.33±0.33 minutes, 16.17±0.65 minutes, 25.50±0.92 minutes and 45.83±1.85 minutes in group B, respectively. Duration of anaesthesia, recovery time, sternal recumbency time, standing time and complete recovery time were significantly (P<0.01) higher in group B compared to group A. The induction dose of tiletamine-zolazepam in group B (1.26±0.02 mg/kg b.wt.) was significantly (P<0.01) lower than group A (6.60±0.06 mg/kg b.wt.). In the animals in group A, excellent muscle relaxation and analgesia was observed at 5 minutes post-induction and up to 60 minutes, whereas in group B, moderate muscle relaxation and excellent analgesia was observed at 5 minutes after premedication followed by excellent muscle relaxation and analgesia at 5 minutes after induction, which persisted up to the end of the anaesthetic period (Table 2). In the animals in group A, palpebral reflex was completely abolished from 15 minutes to 60 minutes post-induction, whereas in group B, the reflex was very weak at 5 minutes after premedication and up to 5 minutes post-induction, followed by complete abolition of reflexes up to the end of the anaesthetic period (Table 2). In the animals in group A, pedal reflex was completely abolished from 10 minutes to 60 minutes post-induction, whereas in group B, the reflex was very weak at 5 minutes after premedication, followed by complete abolition of reflexes up to the end of anaesthetic period (Table 2).

Mean heart rate significantly (P<0.05) increased in the animals in group A at 5 minutes to 30 minutes post-induction, then decreased gradually up to

Table 2. Median±SE of anaesthetic reflexes in animals of both groups

Reflexes	Group	0min	5min after premedication	5min after induction	10min	15min	20min	30min	45min	60min	75min	90min
Muscle relaxation	A	1.00±0.00^{b}	1.00±0.00^{b}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	3.00±0.36^{ab}	1.50±0.34^{b}
	B	1.00±0.00^{b}	3.00±0.00^{b}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}	4.00±0.00^{a}
Palpebral reflex	A	0.00±0.00^{b}	0.00±0.00^{b}	1.00±0.00^{ab}	2.00±0.00^{ab}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	2.00±0.34^{ab}	0.00±0.21^{b}
	B	0.00±0.00^{b}	2.00±0.00^{ab}	2.00±0.00^{ab}	3.00±0.00^{ab}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}
Pedal reflex	A	0.00±0.00^{b}	0.00±0.00^{b}	2.00±0.00^{ab}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	1.50±0.49^{ab}	0.00±0.00^{b}
	B	0.00±0.00^{b}	2.50±0.22^{ab}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}
Analgesia	A	0.00±0.00^{c}	0.00±0.00^{c}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.17^{ab}	2.00±0.36^{abc}	0.50±0.34^{bc}
	B	0.00±0.00^{b}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}	3.00±0.00^{a}

Medians with different superscripts within row differ significantly (P<0.05)

Table 3. Mean±SE of physiological and haemodynamic parameters in animals of both groups

Parameters	Group	Time interval									
		0 min	5 min after premedication	5 min post-induction	15 min	30 min	45 min	60 min	75 min	90 min	180 min
Heart rate (beat/min)	A	88.50±5.39^{b}	102.67±6.98^{ab}	126.00±12.00^{a}	129.00±12.11^{a}	129.67±12.75^{a}	127.67±13.33^{a}	119.50±10.64^{ab}	110.50±9.66^{ab}	100.67±7.20^{ab}	92.00±5.12^{b}
	B	89.50±6.44^{ab}	77.17± 6.20^{b}	95.67±7.74^{ab}	102.33± 8.08^{a}	107.17±8.57^{a}	105.50±8.96^{a}	105.17±8.23^{a}	102.17±7.60^{a}	95.50 ±6.84^{ab}	94.00±5.95^{ab}
Respiration rate (breath/ min)	A	30.00±0.51^{a}	29.50±0.61^{a}	19.17±0.60^{cd}	17.33±0.84^{d}	16.33±1.02^{d}	17.00±0.73^{d}	18.33±0.61^{d}	18.67±0.76^{d}	22.17±0.75^{c}	25.50±0.42^{b}
	B	26.67±1.76^{a}	16.83±1.07^{bc}	10.17±1.76^{d}	10.17±0.70^{d}	13.50±0.22^{cd}	14.67±0.21^{cd}	14.17±1.27^{cd}	18.33±1.52^{bc}	22.50±1.60^{ab}	26.33±0.61^{a}
Rectal temperature (°C)	A	38.56±0.05^{a}	38.50±0.04^{ab}	38.39±0.08^{ab}	38.28±0.10^{ab}	38.22±0.13^{ab}	38.05±0.17^{b}	38.13±0.13^{ab}	38.10±0.12^{ab}	38.21±0.12^{ab}	38.47±0.06^{ab}
	B	38.67±0.06^{a}	38.56±0.07^{ab}	38.47±0.09^{abc}	38.39±0.08^{abc}	38.31±0.08^{abc}	38.12±0.11^{abc}	37.99±0.11^{c}	38.06±0.17^{bc}	38.28±0.18^{abc}	38.51±0.11^{abc}
Systolic arterial blood pressure (mm Hg)	A	134.67±3.46^{ab}	145.17±3.36^{a}	129.50±2.21^{bc}	131.00±2.39^{b}	123.67±2.24^{bcd}	117.67±2.97^{cd}	116.50±3.67^{d}	122.00±1.50^{bcd}	127.33±2.01^{bcd}	134.17±2.98^{ab}
	B	132.67±2.45^{de}	150.50±2.52^{abc}	156.83±2.82^{ab}	162.67±3.08^{a}	157.67±3.09^{ab}	152.33±3.03^{abc}	146.83±3.07^{bc}	141.50±2.79^{cd}	135.17±2.41^{de}	128.00±2.73^{e}
Diastolic arterial blood pressure (mm Hg)	A	83.67±3.46^{ab}	94.17±3.36^{a}	78.50±2.21^{bc}	80.00±2.39^{b}	72.67±2.24^{bcd}	66.67±2.97^{cd}	65.50±3.67^{d}	70.83±1.47^{bcd}	76.17±1.99^{bcd}	83.17±2.91^{ab}
	B	81.67±2.45^{de}	99.50±2.52^{abc}	105.83±2.82^{ab}	111.67±3.08^{a}	106.67±3.09^{ab}	101.33±3.03^{abc}	95.83±3.07^{bc}	90.50±2.79^{cd}	84.17±2.41^{de}	77.00±2.73^{e}
Mean arterial blood pressure (mm Hg)	A	100.17±3.66^{ab}	110.67±3.55^{a}	97.00±1.75^{bc}	96.17±1.97^{bc}	88.83±2.01^{bcd}	82.83±2.91^{d}	81.67±3.54^{d}	86.83±1.53^{cd}	91.83±2.56^{bcd}	97.67±3.48^{abc}
	B	98.17±2.53^{c}	117.67±2.05^{ab}	125.50±2.51^{a}	129.33±2.46^{a}	129.50±3.66^{a}	123.00±3.80^{ab}	115.33±3.98^{ab}	107.50±3.62^{bc}	99.67±3.38^{c}	93.00±4.36^{c}
Haemoglobin oxygen saturation (SpO_2) (%)	A	96.50±0.43^{a}	96.67±0.21^{a}	85.17±1.01^{d}	90.33±1.33^{c}	92.67±0.95^{bc}	95.00±0.45^{ab}	96.00±0.00^{a}	96.17±0.54^{a}	96.67±0.49^{a}	97.00±0.36^{a}
	B	96.50±0.43^{a}	95.67±0.42^{ab}	93.67±0.42^{c}	94.67±0.21^{bc}	95.83±0.31^{ab}	96.67±0.21^{a}	97.00±0.25^{a}	96.83±0.40^{a}	96.67±0.42^{a}	96.50±0.34^{a}

The pairs of values with different superscript vary significantly ($P<0.05$)

180 minutes post-induction compared to the baseline values. In group B, a non-significant (P>0.05) decrease was observed at 5 minutes after premedication, followed by a non-significant (P>0.05) increase at 5 minutes to 30 minutes post-induction compared to baseline values. Thereafter there was a gradual decrease up to 180 minutes in the heart rate of the animals in group B, which came near to the baseline values (Table 3). The mean respiration rate significantly (P<0.05) decreased in the animals in group A at 5 minutes to 30 minutes post-induction compared to the baseline values. Thereafter a gradual increase was observed up to the end of the anaesthetic period which came near to the baseline values. Similarly, a significant (P<0.05) decrease was observed in group B at 5 minutes after premedication to 15 minutes post-induction compared to the baseline values, which thereafter gradually increased after 30 minutes up to the end of anaesthetic period and came near to the baseline values (Table 3). The mean rectal temperature significantly (P<0.05) decreased in the animals in group A at 45 minutes post-induction, then increased gradually up to the end of the anaesthetic period and came near to the baseline values. Similarly, a significant (P<0.05) decrease was observed in the animals in group B at 60 minutes post-induction compared to the baseline values. It increased gradually up to end of the anaesthetic period and came near to the baseline values (Table 3).

Haemodynamic Parameters. Systolic arterial pressure, diastolic arterial pressure and mean arterial pressure were significantly (P<0.05) decreased at 45 minutes to 60 minutes post-induction compared to baseline values, and increased gradually at 75 minutes post-induction up to end of anaesthetic period in the animals in group A. In group B, a significant (P<0.05) increase was observed in the systolic arterial blood pressure, diastolic arterial blood pressure and mean arterial pressure at 5 minutes after premedication up to 60 minutes post-induction compared to the baseline values, followed by gradual decrease from 75 minutes post-induction up to the end of the anaesthetic period (Table 3). Haemoglobin oxygen saturation significantly (P<0.05) decreased at 5 minutes post-induction in the animals of both the groups compared to baseline values. It increased gradually and almost reached the baseline values at the end of anaesthetic period (Table 3). A significant (P<0.05) decrease in the PR interval was recorded at 5 minutes post-induction and 5 minutes after maintenance in the animals in group A compared to baseline values. A significant (P<0.05) increase in QRS interval was recorded at 5 minutes after premedication and 5 minutes after maintenance in the animals in group A, whereas no significant change was recorded in QT interval in the animals in group A as compared to baseline values. Non-significant changes were recorded in the PR interval, QRS interval and QT interval in the animals in group B at the respective time interval (Table 4).

Biochemical Parameters. A significant (P<0.05) increase in serum glucose was recorded at 30 minutes to 1 hour in both the groups of animals compared to baseline values. A non-significant (P>0.05) decrease in serum total protein and serum albumin was recorded at 30 minutes to 1 hour in both the groups of animals compared to baseline values. Similarly, a non-significant (P>0.05) de-

Table 4. Recording of electrocardiographic parameters in animals of both groups (Mean±SE)

Parameters	Groups	0	5 min after premedication	5 min post-induction	5 min after maintenance
PR interval (seconds)	A	0.109±0.006[a]	0.091±0.005[ab]	0.083±0.003[b]	0.071±0.005[b]
	B	0.1±0.02	0.113±0.027	0.093±0.027	0.1±0.023
QRS interval (seconds)	A	0.045±0.005[b]	0.046±0.005[a]	0.045±0.00[b]	0.047±0.00[a]
	B	0.064±0.003	0.08±0.012	0.062±0.010	0.068±0.006
QT interval (seconds)	A	0.212±0.014	0.207±0.014	0.193±0.014	0.191±0.015
	B	0.213±0.013	0.24±0.02	0.209±0.016	0.209±0.011

The pairs of values with different superscripts vary significantly (P<0.05)

Table 5. Recording of biochemical parameters in animals of both groups (Mean±SE)

Parameters	Groups	Time interval (Hours)				
		0	0.5	1	6	24
Glucose (mg/dl)	A	71.21±1.53^{c}	83.50±1.22^{b}	89.13±1.43^{a}	82.87±0.88^{b}	74.73±1.47^{c}
	B	71.24±0.98^{d}	89.66±0.88^{b}	98.41±0.47^{a}	95.71±0.87^{a}	79.91±1.04^{c}
Total protein (g/L)	A	64.7±0.31	63.1±0.31	62.5±0.32	62.9±0.32	63.9±0.31
	B	65.2±0.31	61.2±0.32	60.2±0.31	62.2±0.32	64.6±0.32
Serum albumin (g/L)	A	29.4±0.11	27.1±0.10	26.4±0.11	26.9±0.11	28.3±0.10
	B	29.6±0.10	25.7±0.08	24.5±0.06	25.9±0.08	28.5±0.09
Serum urea nitrogen (mg/dl)	A	21.18±0.83	19.48±0.83	19.41±0.83	19.94±0.85	21.97±0.84
	B	21.28±0.83	20.65±0.83	21.00±0.78	21.26±0.80	21.74±0.89
Serum creatinine (mg/dl)	A	1.27±0.10	1.19±0.10	1.22±0.10	1.21±0.11	1.21±0.11
	B	1.29±0.08	1.26±0.08	1.28±0.09	1.26±0.08	1.22±0.07
Serum alanine amino transferase (U/L)	A	34.64±1.38	32.11±1.44	32.81±1.46	33.03±1.47	33.38±1.45
	B	35.28±0.85	32.45±0.91	33.34±0.85	33.51±0.96	35.05±0.87
Serum aspartate amino transferase (U/L)	A	27.39±2.76	25.87±1.92	26.51±1.87	26.44±1.82	26.19±1.79
	B	26.63±1.75	24.67±1.71	25.51±1.62	25.54±1.53	25.64±1.71

The pairs of values with different superscripts vary significantly (P<0.05)

crease in serum urea nitrogen was observed at 30 minutes to 1 hour in group A, whereas a non-significant (P>0.05) decrease was recorded at 30 minutes in the animals in group B. Non-significant (P>0.05) decreases in serum creatinine, ALT and AST were recorded at 30 minutes in animals in both groups compared to baseline values. All the parameters in both groups were near to baseline values after a 24 hour period (Table 5).

Discussion and conclusions

Preanaesthetic administration of dexmedetomidine and butorphanol enhanced the quality of induction in the animals in group B, which might be due to their sedative, adequate muscle relaxation and analgesic properties. A similar finding was also reported by RAFEE et al. (2015); KUMAR et al. (2016) and KOLI et al. (2021), after administration of sedative and analgesic drugs. There was a significant (P<0.01) increase in the duration of anaesthesia, recovery time, sternal recumbency time, standing time and complete recovery time in the animals in group B compared to group A, which might be due to the synergistic effects of dexmedetomidine, butorphanol and tiletamine. Tiletamine inhibits pain by blocking the NMDA receptors non-competitively, and prolongs the duration of anaesthesia and the recovery period in the animals, which might be due to the longer plasma half-life of the drug. The additive effect of dexmedetomidine and butorphanol enhances the induction quality, the duration of anaesthesia and recovery in the animals in group B, which might be due to the longer tranquilizing and sedative effect, and adequate muscle relaxation and analgesic effects of the drugs. Dexmedetomidine has very high selectivity for α-2 receptors, and augments depression of the central nervous system, thereby releasing their sedative and analgesic properties (KUKANIC and PAPICH, 2017). The analgesic and sedative effect of butorphanol is due to the μ1 and μ2 receptors that act above and within the level of the spinal cord (BOOTHE, 2001). Similar results were also reported by RAFEE et al. (2015) and HAMPTON et al. (2019) after preanaesthetic administration of sedative and analgesic drugs. A significant (P<0.01) reduction was observed in the induction dose needed for the animals in group B which might be due to the sedative and analgesic effects of dexmedetomidine and butorphanol, which confirms the finding of JADON et al. (1998) and

KUMAR et al. (2016). In group B, the moderate muscle relaxation after premedication might be due to the alpha-2 agonist property of dexmedetomidine, which is attributed to inhibition of the intraneuronal transmission of impulses at the level of the central nervous system (MARJORIE, 2001; LEMKE, 2007). A similar finding was also reported by JADON et al. (1995) in dogs administered atropine detomidine-ketamine. However, co-administration of tiletamine-zolazepam and sevoflurane along with dexmedetomidine enhanced the duration and quality of muscle relaxation. Prolonged duration and improved quality of analgesia were observed in the animals in group B, which might be due to the effect of combined butorphanol, dexmedetomidine, tiletamine and inhalant anaesthesia (JENA et al., 2014; HAMPTON et al., 2019; RATNU et al., 2021). Complete abolition of pedal and palpebral reflexes during maintenance with sevoflurane inhalant anaesthesia was recorded in the animals induced with tiletamine-zolazepam, which confirms the findings of RATNU et al. (2021). In the animals in group B, reflexes were greatly suppressed for a longer period, which might be due to the synergistic effect of the drugs administered along with dexmedetomidine and butorphanol (SHARMA et al., 2014; JENA et al., 2014).

The initial increase in the heart rate of the animals in group A might be due to the combined sympathetic-stimulating effect of tiletamine and the vagolytic effect of atropine sulphate, whereas premedication with dexmedetomidine reduced the heart rate of the animals in group B, which might be due to the properties of the alpha 2 agonist. A similar finding was also reported by SABBE et al. (1994); CHEN et al. (2005) and SAVVAS et al. (2005). The decrease in respiration rate of the animals in both the groups after induction might be due to the effect of tiletamine. The respiratory depressant effect of the α-2 agonist is likely to be exaggerated when used in combination with other anaesthetic agents (JADON et al., 1998; KUSHIRO et al., 2005; RATNU et al., 2021). The decrease in rectal temperature in both the groups of animals might be attributed to reduced heat production due to the decreased metabolic rate during anaesthe- sia, or by action of the drug on the hypothalamus or the reduction in peripheral circulation, or due to muscle relaxation, the effect of central alpha-2 adrenoceptors on thermoregulatory centre (AHMAD et al., 2013; KUMAR et al., 2016) or heat loss through the abdominal cavity during surgeries performed such as ovariohysterectomy, laparotomy and cystotomy.

The initial increase in systemic blood pressure in both groups of animals was due to the administration of atropine sulphate and stimulation of peripheral α-2 agonist receptors by premedication with dexmedetomidine (VAINIO and PALMU, 1989; BISHT et al., 2018; TIWARI et al., 2021), whereas the decrease in systemic blood pressure after the administration of tiletamine-zolazepam might be due to a significant decrease in the peripheral vascular resistance (HELLYER et al., 1989; NAM et al., 2013). A significant ($P<0.05$) decrease in haemoglobin oxygen saturation was observed in both groups of animals after the administration of the induction agent tiletamine-zolazepam, which confirms the finding of SAVVAS et al. (2005) and CHEN et al. (2005). Post-induction apnoea and respiratory depression were the major adverse effects which occurred shortly after intravenous administration of tiletamine-zolazepam without premedication, but they resolved within minutes. Premedication with dexmedetomidine and butorphanol reduces the induction dose of tiletamine-zolazepam, and thus reduces post-induction apnoea and respiratory depression to some extent. A significant ($P<0.05$) decrease in the PR interval was recorded post-induction and after maintenance in the animals in group A compared to baseline values. This reduction in PR interval was due to an increase in heart rate caused by atropine sulphate and tiletamine, which reflects the increase in the conductivity of the cardiac stimuli between the sinus node and the atrioventricular node. A similar finding was also reported by TARRAGA et al. (2000) in animals anesthetized with atropine-tiletamine-zolazepam.

The significant ($P<0.05$) increase in serum glucose in both groups of animals compared to baseline values might be due to glycogenolysis in the liver during the anaesthetic period. The increase in serum glucose in the animals in group B might also be due to suppression of insulin by the alpha-2 ag-

onist. A similar finding was reported by BOUGHERARA and BOUAZIZ (2014). The non-significant (P>0.05) decrease in the serum total protein and serum albumin might be due to inter compartmental shifting of fluid, causing haemodilution. The non-significant (P>0.05) decrease in serum urea nitrogen and serum creatinine reveals the less adverse effect of anaesthesia on renal perfusion, whereas the non-significant (P>0.05) decrease in ALT and AST indicates the less deleterious effect of these anaesthetic combinations on the liver. Similar findings were also reported by DUZGUN et al. (2004) and KOLI et al. (2021).

Both anaesthetic combinations produced satisfactory anaesthesia with transient changes in clinicophysiological, haemodynamic and biochemical parameters. However, the combination of dexmedetomidine @ 5 µg/kg body weight and butorphanol @ 0.1 mg/kg body weight, along with atropine-tiletamine-zolazepam-sevoflurane anaesthesia produced excellent muscle relaxation and analgesia, with complete abolition of pedal and palpebral reflexes, and was found to be better compared to the atropine-tiletamine-zolazepam-sevoflurane anaesthesia.

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SAŽETAK

Istraživanje provedeno na 12 kliničkih pacijenata neovisno o dobi, pasmini i spolu, koji su nasumično podijeljeni u dvije skupine (A i B) sa po 6 pasa. Psi u skupini A dobili su premedikaciju atropin-sulfatom u dozi od 0,04 mg/kg tjelesne mase supkutano. Isto je učinjeno i sa psima skupine B koji su još primili deksmedetomidin u dozi od 5 µg/kg tjelesne mase intravenski u 5-minutnim intervalima, te nakon toga još i butorfanol u dozi od 0,1 mg/kg tjelesne mase intravenski u 10-minutnim intervalima. Tiletamin-zolazepam primijenjen je intravenski kao indukcijsko sredstvo do uvoda u anesteziju, a održavanje je provedeno sevofluranom u obje istraživanje skupine. U obje su skupine pasa procijenjeni kliničko-fiziološki hemodinamički i biokemijski pokazatelji u različitim intervalima. Vrijeme indukcije u anesteziju bilo je statistički znakovito kraće ($P<0,01$), dok je trajanje anestezije, vrijeme sternalnog ležanja, vrijeme stajanja, vrijeme oporavka i potpuno vrijeme oporavka bilo znakovito dulji ($P<0,01$) u pasa skupine B u usporedbi sa skupinom A. Uočen je izvrstan učinak u relaksaciji mišića i analgeziji u pasa u skupini B u odnosu na one u skupini A. Ukidanje pedalnog i palpebralnog refleksa bilo je bolje u pasa skupine B u usporedbi sa skupinom A. Fiziološki pokazatelji kolebali su unutar referentnih raspona. U pasa skupine A zabilježeni su znakovito smanjenje ($P<0,05$) PR intervala i znakovito povećanje ($P<0,05$) QRS intervala. Znakovit porast ($P<0,05$) serumske glukoze i neznakovito smanjenje ($P>0,05$) serumskog albumina, ukupnih proteina u serumu, serumske ureje i kreatinina zabilježeni su u obje istraživae skupine. Zaključeno je da, u kliničkih pacijenata u kojih se obavljaju rutinski kirurški zahvati, anestetička kombinacija atropin-deksmedetomidin-butorfanol-tiletamin-zolazepam-sevoflurana pruža bolje uravnoteženu anesteziju u usporedbi s kombinacijom atropin-tiletamin-zolazepam-sevofluran.

Ključne riječi: anestezija; tiletamin-zolazepam; deksmedetomidin; butorfanol; sevoflurane; psi