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# Clinicophysiological and hematobiochemical effect of dexmedetomidine or diazepam with ketamine and propofol in total intravenous anesthesia in goats

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## Abstract

**Background:** Total intravenous anesthesia (TIVA) is a well-documented anesthetic concept for some animal species, including dogs and horses; however, information about TIVA protocols in goats is currently inadequate. Therefore, this study aimed to compare the clinicophysiological and hematobiochemical effects of dexmedetomidine (DEX) and diazepam premedication with ketamine and propofol.

**Result:** The DEX-treated group showed a significantly decreased heart rate compared with the diazepam-treated group. Onset of anesthesia and sedation in group I was significantly faster than that in group II (0.33 ± 0.08 and 0.25 ± 0.08 min vs. 3.33 ± 1.53 and 2.0 ± 1.0 min, respectively). Duration of anesthesia and sedation in group I was significantly longer than that in group II (66.67 ± 7.64 and 161.3 ± 43.3 min vs. 37.0 ± 5.19 and 60.33 ± 7.57 min, respectively). The total recovery period in group II was significantly shorter than that in group I (47.0 ± 7.21 vs. 98.33 ± 15.27 min).

Smooth induction and recovery occurred in all goats in group I, whereas most goats in group II exhibited slightly prolonged induction with mild excitation and presence of swallowing reflex and prolonged struggling during recovery.

**Conclusion:** In TIVA, premedication with DEX produces excellent quality anesthesia, analgesia, sedation, and muscle relaxation. Furthermore, it produces a longer duration of anesthesia, sedation, and analgesia than premedication with diazepam. For these reasons, DEX is more suitable for long surgical procedures, whereas diazepam can be used in minor surgical procedures in goats. Both drug combinations produce hemodynamic stability.

**Keywords:** Dexmedetomidine, Diazepam, Goat, Ketamine, Propofol

## 1 Background

Perfect anesthesia is necessary for a successful surgery to produce relaxation, immobilization, and unconsciousness. Despite the availability of new anesthetic and analgesic drugs, none of them achieves the qualities of an ideal anesthetic and analgesic agent. Therefore, the combination of sedatives and anesthetic agents has been broadly used in animal practice to achieve optimum analgesia, hypnosis, and muscle relaxation [1]. Although ruminants commonly endure several surgical interferences under physical restraint, sedation, and local or regional anesthesia, general anesthesia could be favored over other procedures, particularly during complex and prolonged surgical interferences that require complete control of movement and pain during surgery. Several types of anesthetic drugs are used in small ruminant anesthesia; however, precautions are observed during anesthesia, and balanced anesthesia is typically applied to

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diminish complications. The balanced anesthetic protocol comprises a combination of drugs that produce general anesthetic effects with minimal adverse effects on cardiopulmonary function compared with the use of one drug alone [2]. Surgical management of animals needs safe pre-anesthetics and ideal anesthetic agents that produce deep sleep, analgesia, amnesia, and muscle relaxation. A suitable pre-anesthetic treatment may produce cardiovascular stability, good sedation, excellent analgesia, and better recovery from anesthesia. Pre-anesthetic treatment directly affects the dose of anesthetic agents that may result in least complication due to low anesthesia intake. Different sedatives (xylazine, detomidine, DEX, diazepam, midazolam, and butorphanol) are being used nowadays as pre-anesthetic agents [3].

DEX is a highly selective alpha 2 (α2)-adrenoceptor agonist with powerful analgesic and sedative properties. DEX is commonly used in small animals as premedication in balanced anesthesia. It provides sedative properties resembling natural sleep, with minimal respiratory depression. Furthermore, it has a significant influence on requirements of anesthesia, including a sparing effect on the minimal alveolar concentration during inhalation anesthesia. DEX is commonly used with opioids to achieve a synergistic effect that leads to a decreased dose of the combinations [4]. In previous literature, a total intravenous (IV) anesthetic protocol containing propofol, ketamine, and DEX was found to provide stable cardiovascular conditions and excellent antinociception in healthy pigs; these advantages are important in anesthesia during invasive surgical procedures in experimental animals [5].

Diazepam is a benzodiazepine derivative. It has anxiolytic, skeletal muscle relaxation, hypnotic, anticonvulsant, and sedative properties. A combination of diazepam and ketamine with or without xylazine is widely used to produce general anesthesia in small ruminants [6]. Despite the usefulness of diazepam/ketamine combination, this, when used in goats, produced short duration anesthesia and inadequate analgesia [7].

To the best of our knowledge, the combination of DEX with ketamine and propofol in one regimen has not been applied before in goats; therefore, this study aimed to investigate the clinicophysiological and hematobiochemical effects of DEX, ketamine, and propofol combination and compare the results with that of customary diazepam, ketamine, and propofol regimen.

## 2 Methods

This study was conducted in the Surgery, Anesthesiology, and Radiology Department, Faculty of Veterinary Medicine, Beni-Suef University, Beni-Suef, Egypt.

### 2.1 Drugs

- Atropine sulfate 1% solution 2 mL (Atropine®; Sigma Tec Pharmaceuticals)
- Diazepam 10 mg (Neuril®; Memphis Pharmaceuticals and Chemical Industries)
- DEX hydrochloride 200 µg/2 mL (Precedex; Hospira, NC, USA)
- Ketamine 50 mg/mL (Ketamine®; Sigma Tec Pharmaceuticals)
- Propofol 10 mg/mL (Lipuro®; B. Braun Melsungen AG, Melsungen, Germany)

### 2.2 Animals

Six native, female nonpregnant goats were used. Their body weight ranged from 22 to 30 kg, and their age ranged between 2 and 3 years. The animals were treated with broad-spectrum antiparasitic drugs 3 weeks before commencing the experiments. All goats were housed under the same husbandry as well as similar nutritional and management conditions in a group pen. The goats were fed daily with a constant mixture containing mainly alfalfa hay and corn, supplemented with minerals. Freshwater was also provided. Before the beginning of the experiment, feed and water were withdrawn for 12 and 8 h, respectively. At each experiment day, the skin over the left jugular vein was clipped and scrubbed with povidone-iodine for IV anesthesia administration using a 20-gauge catheter that was introduced percutaneously into the jugular vein of each goat. All goats were apparently healthy based on clinical examination before anesthesia.

The goats received atropine at a dose of 0.05 mg/kg of body weight intramuscularly.

### 2.3 Experimental design

The goats were divided into two groups consisting of three animals each.

Group I: DEX (3 µg/kg of body weight) was injected over 2 min following dilution with 0.9% sodium chloride solution to achieve a 4-µg/mL concentration prior to administration.

Group II: diazepam was administered at a dose of 0.5 mg/kg of body weight.

After 10 min, anesthesia was achieved by ketamine (6 mg/kg of body weight) and maintained by propofol administration (5 mg/kg of body weight) in both groups. All drugs were administered by slow IV injection.

### 2.4 Assessment of anesthesia

The anesthetic effect was assessed depending on physiological, clinical, and hematobiochemical parameters.

#### *2.4.1 Clinical parameters*

The onset and duration of anesthesia and sedation, total recovery period, and quality of induction and recovery were recorded. Moreover, jaw relaxation, pedal and palpebral reflexes, and sedation scoring were evaluated according to the scoring systems presented in Tables 1 and 2, respectively.

Onset of anesthesia was defined as the time interval between the injection of drug and absence of reflexes, whereas duration of anesthesia was defined as the time interval from the absence of reflexes to the return of reflexes. The total recovery period was calculated as the time interval from the absence of reflexes to animal standing. Muscular relaxation and absence of swallowing reflexes were used to determine the onset of anesthesia. Pinching the skin and underlying tissue with sterile needle and hemostatic forceps were performed to check anesthesia depth. The anesthetized animals were then positioned on the right side. Their heads were elevated to allow free drainage of saliva [6].

*2.4.1.1 Induction quality* Good: induction was smooth, rapidly returned to the recumbent position, and absence of any excitement.

Fair: induction was slightly prolonged, excitation was mild, and swallowing reflex was present.

Poor: excitement was obvious, animal jumped or attempted to stand after recumbency, and full swallowing reflex was present.

*2.4.1.2 Recovery quality* Good: recovery was smooth, the animal easily returned to alertness, sternal position recurred, stood up within a short time, and walked with less ataxia.

Fair: transient excitation or movement of the whole body, some struggling was observed, excessive response that disappeared as soon as animal stood up unaided, and with moderate ataxia.

Poor: stereotype behavior as circular movement, premature trials to stand, and struggling was prolonged.

**Table 2** Five-Point Sedation Scale

| Score | Description |
|---|---|
| 1 | No sedation (goat appears unchanged from initial attitude) |
| 2 | Low head carriage, "droopy eyelid," ptyalism, and decreased reaction to external stimuli |
| 3 | Head lowers toward the ground and swaying of hind legs |
| 4 | Attempts to lie down but aroused with stimulation |
| 5 | Recumbency and unresponsive to external stimuli |

#### *2.4.2 Physiological parameters*

The heart rate (HR, beats/min) was determined by counting the heartbeats over the cardiac area using a stethoscope. The respiratory rate (RR, breaths/min) was measured by placing a stethoscope on the trachea. Rectal temperature (RT, °C) was recorded by a digital thermometer at 0 min (baseline) and subsequently after premedication, induction, and at 5, 10, 15, 20, 30, 45, 60, and 120 min after drug administration.

#### *2.4.3 Hematobiochemical parameters*

Blood samples were drawn from the jugular vein at 0, 15, 30, 60, 120, and 240 min from drug administration. EDTA, heparin (for blood gases analysis), and sodium fluoride (for glucose) were used to obtain plasma.

*2.4.3.1 Analysis* Hemoglobin (Hb) levels were determined using Sahli's method, and values were expressed in gm% [8]. Packed cell volume (PCV) was evaluated using the microhematocrit method [9], and values were expressed as percentages. Red blood cell count (RBC) was measured using the procedure described by Jain [10], and values were expressed in million cells per microliter. Blood urea nitrogen (BUN) (mg/dL) was estimated using the enzymatic colorimetric method [11]. Serum alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase was estimated using the alanine aminotransferase-liquizyme, and values were expressed in U/L [12]. Serum aspartate aminotransferase (AST)/

**Table 1** Numeric scoring system applied to estimate several reflexes

| Clinical parameter | Score | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| Jaw relaxation | Not permitting jaw opening | The animal resists opening and closes its jaw rapidly | The animal has less resistance to opening its jaw and wraps it slowly | There is no resistance and the jaw still opens |
| Palpebral reflex | Intact and robust (rapid blink) | Intact but weak (slow response) | Intact but very light (slow and occasionally response) | Abolished |
| Pedal reflex | Intact and powerful (potent withdrawal) | Intact but weak (animal response slowly) | Intact but very light (slow and occasional response) | Abolished completely |

serum glutamic oxaloacetic transaminase was estimated using the aspartate aminotransferase IFCC method, and values were expressed in U/L. Serum glucose level (mg/dL) was estimated using the enzymatic colorimetric method (GOD-POD) according to the manufacturer's instructions. Creatinine was measured, and values were expressed in mg/dL. Cortisol concentration (μg/dL) was estimated using Cortisol ELISA kits (Immunospec Corporation, CA, USA). For blood gases, samples of central venous blood were carefully withdrawn into airtight 3-mL heparinized plastic syringes. They were kept on ice until analyzed within 10 min using a blood gas analyzer (model 178; Corning Medical and Scientific, Medfield, MA, USA).

### 2.5 Statistical analysis

Data were analyzed using different statistical methods. Biochemical and physiological parameters were analyzed using two-way mixed design analysis of variance (ANOVA), wherein the effect of treatment was fitted as the between-subjects factor, and the effect of time was fitted as the within-subjects factor of repeated measures. Additionally, the interaction between the treatment and time intervals was considered. All biochemical and physiological parameters in the form of means ± standard deviations (SDs) along with significance indices are presented in tables. Clinical parameters were analyzed using nonparametric approaches, such as Kruskal–Wallis and Freidman's tests of ANOVA, followed by confirmatory parametric ANOVA procedures. Clinical parameters are demonstrated in tables as means and mean ranks instead of SD. Graphical presentation of all studied parameters was applied using line and bar charts, assuming the time intervals as the horizontal axis. Furthermore, qualitative data were analyzed using the Chi-square test of categorical data. Statistical analyses were conducted using SPSS, SAS, and MSTAT-C software. Qualitative data that revealed no statistical importance are presented in the tables in the form of category description for studied groups. Results were considered significant for every probability $\leq 0.05$ ($P \leq 0.05$).

## 3 Results

### 3.1 Hematobiochemical parameters

PH gradually decreased; however, it remained significantly lower than the baseline value after anesthesia induction up to 30 min of the observation period in both groups ($p < 0.05$). Subsequently, PH significantly increased compared with the baseline value at 120 min in group I ($p < 0.05$). Thereafter, a comparison between both groups revealed that the mean PH was significantly lower at 15 min and onward up to 120 min in group II ($p < 0.05$) (Table 3). Partial pressure of carbon dioxide ($pCO_2$) significantly increased at 30 min in both groups ($p < 0.05$), significantly decreased at 120 min in group I ($p < 0.05$), and did not significantly increase at the rest of time intervals in both groups ($p > 0.05$) (Table 3). Partial pressure of oxygen significantly increased at 15, 60, and 240 min in group I and 240 min in group II ($p < 0.05$) (Table 3). The

**Table 3** Mean ± standard deviation (SD) of hematobiochemical parameters at different time intervals

| Parameter | | Time (min) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | 15 | 30 | 60 | 120 | 240 |
| PH | Group I | $7.42^{bc} \pm 0.01$ | $7.37^{e} \pm 0.01$ | $7.28^{g} \pm 0.01$ | $7.41^{bc} \pm 0.01$ | $7.47^{a} \pm 0.01$ | $7.40^{cd} \pm 0.01$ |
| | Group II | $7.42^{bc} \pm 0.01$ | $7.33^{f} \pm 0.01$ | $7.34^{f} \pm 0.01$ | $7.40^{cd} \pm 0.01$ | $7.38^{de} \pm 0.01$ | $7.43^{b} \pm 0.03$ |
| $PCO_2$ (mmHg) | Group I | $42.80^{bc} \pm 3.15$ | $49.77^{abc} \pm 3.60$ | $54.91^{a} \pm 4.04$ | $44.30^{bc} \pm 3.25$ | $34.90^{d} \pm 2.55$ | $44.10^{bc} \pm 3.25$ |
| | Group II | $42.0^{c} \pm 4.39$ | $45.73^{bc} \pm 4.79$ | $50.57^{ab} \pm 5.29$ | $44.13^{bc} \pm 4.59$ | $43.20^{bc} \pm 4.49$ | $42.80^{bc} \pm 3.93$ |
| $PO_2$ (mmHg) | Group I | $34.67^{de} \pm 3.21$ | $51.67^{b} \pm 4.93$ | $38.88^{cde} \pm 3.41$ | $62.67^{a} \pm 5.85$ | $31.0^{e} \pm 2.64$ | $47.49^{bc} \pm 4.41$ |
| | Group II | $39.67^{cde} \pm 5.51$ | $43.97^{bcd} \pm 6.11$ | $47.17^{bc} \pm 6.55$ | $38.60^{cde} \pm 5.39$ | $48.67^{bc} \pm 6.75$ | $53.67^{ab} \pm 7.23$ |
| $HCO_3$ (mmol/L) | Group I | $26.03^{ab} \pm 1.05$ | $29.27^{a} \pm 1.20$ | $26.74^{ab} \pm 1.08$ | $28.73^{a} \pm 1.15$ | $27.17^{ab} \pm 2.15$ | $28.72^{a} \pm 1.16$ |
| | Group II | $25.0^{b} \pm 2.10$ | $26.50^{ab} \pm 2.20$ | $24.93^{b} \pm 2.10$ | $25.10^{b} \pm 2.10$ | $28.70^{a} \pm 2.40$ | $27.0^{ab} \pm 2.0$ |
| $SO_2$ (%) | Group I | $66.46^{cde} \pm 9.22$ | $81.80^{abc} \pm 11.34$ | $58.38^{e} \pm 8.11$ | $87.73^{a} \pm 12.15$ | $64.86^{de} \pm 8.95$ | $76.04^{abcd} \pm 10.5$ |
| | Group II | $75.16^{abcd} \pm 6.02$ | $85.60^{ab} \pm 6.87$ | $69.93^{bcde} \pm 5.61$ | $63.33^{de} \pm 5.08$ | $87.07^{a} \pm 6.98$ | $85.93^{a} \pm 6.98$ |
| Glucose (mg/dL) | Group I | $89.33^{c} \pm 17.09$ | $176.3^{abc} \pm 33.6$ | $234.3^{a} \pm 39.11$ | $195.0^{ab} \pm 37.40$ | $137.0^{ab} \pm 26.1$ | $87.0^{c} \pm 15.72$ |
| | Group II | $113.7^{bc} \pm 57.01$ | $118.3^{bc} \pm 59.5$ | $152.3^{abc} \pm 76.5$ | $148.3^{abc} \pm 74.5$ | $109.3^{bc} \pm 55.0$ | $88.7^{c} \pm 44.95$ |
| BUN (mg/dL) | Group I | $34.0^{b} \pm 2.64$ | $35.0^{b} \pm 2.64$ | $39.0^{ab} \pm 3.60$ | $40.0^{ab} \pm 3.60$ | $33.0^{b} \pm 2.64$ | $40.0^{ab} \pm 3.0$ |
| | Group II | $40.6^{ab} \pm 15.04$ | $44.2^{ab} \pm 16.34$ | $59.0^{ab} \pm 21.70$ | $55.3^{ab} \pm 20.56$ | $66.7^{a} \pm 24.58$ | $59.0^{ab} \pm 21.70$ |
| Creatinine (mg/dL) | Group I | $1.17^{a} \pm 0.56$ | $1.03^{a} \pm 0.35$ | $0.83^{a} \pm 0.40$ | $0.93^{a} \pm 0.42$ | $1.03^{a} \pm 0.51$ | $1.30^{a} \pm 0.62$ |
| | Group II | $0.83^{a} \pm 0.15$ | $0.83^{a} \pm 0.15$ | $0.83^{a} \pm 0.15$ | $0.83^{a} \pm 0.15$ | $0.93^{a} \pm 0.15$ | $0.73^{a} \pm 0.15$ |

Within each comparison, means with different superscripts are statistically significant at a 0.05 level of significance ($P < 0.05$). Small letters represent the interaction effects of both treatment and time. Capital letters represent the overall significance (main effect of treatment and main effect of time)

bicarbonate ($HCO_3$) value did not significantly increase up to the end of the observation period in both groups; however, it significantly increased at 120 min in group II ($p < 0.05$) (Table 3). Oxygen saturation did not significantly differ in both groups, except at 60 min wherein it significantly increased in group I ($p < 0.05$) (Table 3).

Glucose significantly increased at 30 and 120 min in group I ($p < 0.05$), whereas no significant change was observed in group II. Comparison among the groups did not reveal any significant difference in plasma glucose values at different time intervals (Table 3). Urea and creatinine did not significantly differ in both groups ($p > 0.05$) (Table 3). AST did not demonstrate significant changes in both groups. A significant increase in ALT at 30 and 60 min was noted in group II ($p < 0.05$), whereas no significant difference was noted in group I ($p > 0.05$) (Table 4). Hb values did not significantly decrease until 60 min in both groups ($p < 0.05$); however, they significantly decreased at 120 min in group I, whereas the reduction continued significantly to 240 min in group II. A gradual reduction in PCV in both groups was observed, which became significant at 120 min in group I and until 240 min in group II ($p < 0.05$). RBC values did not show a significant decrease in both groups. Cortisol values did not show a significant change in group II, whereas a significant increase was observed in group I at 30 and 60 min ($p < 0.05$) (Table 4). Normal range values are provided in Additional file 1: Table S1.

### 3.2 Physiological parameters

RT did not significantly decrease after DEX premedication ($p < 0.05$). However, after anesthesia induction, RT significantly decreased until the end of the observation period in group I, whereas a nonsignificant decrease in temperature that remained at most intervals until the end of the observation period in group II was observed ($p < 0.05$). RR did not significantly change in both groups until the end of the observation period ($p > 0.05$). HR significantly decreased after DEX premedication and after anesthesia induction at 20 and 30 min in group I ($p < 0.05$), whereas HR values did not significantly change until the end of the experiment in group II ($p > 0.05$) (Table 5). Normal range values are provided in Additional file 1: Table S1.

### 3.3 Clinical parameters

The anesthetic effects of IV DEX, ketamine, and propofol combination (group I) after ketamine IV injection revealed that the mean ± SD values of onset of anesthesia, duration of anesthesia, onset of sedation, and duration of sedation were 0.33 ± 0.08, 66.67 ± 7.64, 0.25 ± 0.08, and 161.3 ± 43.3 min, respectively, whereas that for the total recovery period was 98.33 ± 15.27 min. The anesthetic effects of IV injection of diazepam, ketamine, and propofol combination (group II) revealed that the mean ± SD values of onset of anesthesia, duration of anesthesia, onset of sedation, and duration of sedation were 3.33 ± 1.53, 37.0 ± 5.19, 2.0 ± 1.0, and 60.33 ± 7.57 min, respectively, whereas that for the total recovery period was 47.0 ± 7.21 min. The results suggested that group I showed significantly rapid onset of anesthesia and sedation and longer duration of anesthesia and sedation ($p < 0.05$, $p < 0.01$, and $p < 0.05$, respectively) than group II. Following the administration of anesthetics, smooth induction was observed in all animals of group I, whereas most goats

**Table 4** Mean ± standard deviation (SD) of hematobiochemical parameters at different time intervals

| Parameter | Group | Time (min) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | 15 | 30 | 60 | 120 | 240 |
| AST (U/L) | Group I | $68.67^{abc} \pm 17.55$ | $55.67^{bc} \pm 7.09$ | $55.33^{bc} \pm 10.96$ | $50.67^{c} \pm 9.45$ | $84.33^{a} \pm 21.59$ | $69.67^{abc} \pm 18.55$ |
| | Group II | $84.0^{a} \pm 11.53$ | $87.67^{a} \pm 12.09$ | $77.67^{ab} \pm 10.40$ | $76.67^{ab} \pm 10.40$ | $68.67^{abc} \pm 9.45$ | $66.33^{abc} \pm 9.07$ |
| ALT (U/L) | Group I | $21.0^{cde} \pm 2.64$ | $27.33^{abc} \pm 3.21$ | $24.33^{bcd} \pm 4.04$ | $17.67^{de} \pm 2.08$ | $14.33^{e} \pm 2.08$ | $20.33^{cde} \pm 1.52$ |
| | Group II | $22.67^{cde} \pm 5.68$ | $21.0^{cde} \pm 5.56$ | $31.33^{ab} \pm 7.76$ | $33.67^{a} \pm 8.32$ | $16.33^{de} \pm 4.16$ | $15.0^{e} \pm 3.60$ |
| Hb (gm%) | Group I | $10.40^{a} \pm 1.31$ | $9.96^{a} \pm 1.26$ | $9.30^{ab} \pm 1.49$ | $8.67^{abcd} \pm 1.59$ | $7.23^{bcd} \pm 1.06$ | $9.13^{ab} \pm 1.17$ |
| | Group II | $10.63^{a} \pm 1.50$ | $8.70^{abcd} \pm 1.21$ | $8.97^{abc} \pm 1.27$ | $9.60^{ab} \pm 1.38$ | $6.43^{d} \pm 0.89$ | $6.60^{cd} \pm 0.95$ |
| PCV (%) | Group I | $29.67^{abc} \pm 5.24$ | $26.87^{abcd} \pm 4.4$ | $26.53^{abcd} \pm 4.8$ | $22.20^{cd} \pm 3.26$ | $20.07^{d} \pm 2.71$ | $30.30^{ab} \pm 3.14$ |
| | Group II | $34.36^{a} \pm 5.03$ | $27.40^{abcd} \pm 4.0$ | $27.56^{abcd} \pm 4.1$ | $28.36^{abc} \pm 4.16$ | $22.36^{cd} \pm 3.29$ | $23.20^{bcd} \pm 3.51$ |
| RBCs ($10^6$/μL) | Group I | $20.26^{a} \pm 2.15$ | $15.07^{a} \pm 0.92$ | $17.35^{a} \pm 1.12$ | $16.15^{a} \pm 1.03$ | $18.15^{a} \pm 1.45$ | $21.28^{a} \pm 2.43$ |
| | Group II | $21.84^{a} \pm 8.32$ | $14.91^{a} \pm 5.68$ | $17.17^{a} \pm 6.54$ | $17.47^{a} \pm 6.66$ | $15.34^{a} \pm 5.82$ | $14.92^{a} \pm 5.68$ |
| Cortisol (μg/dL) | Group I | $2.88^{d} \pm 1.91$ | $4.62^{cd} \pm 1.55$ | $8.42^{ab} \pm 1.13$ | $7.27^{ab} \pm 1.12$ | $3.70^{d} \pm 2.46$ | $2.93^{d} \pm 1.95$ |
| | Group II | $6.58^{abc} \pm 0.39$ | $6.17^{bc} \pm 0.35$ | $6.90^{abc} \pm 0.40$ | $7.13^{ab} \pm 0.45$ | $8.73^{a} \pm 0.50$ | $8.73^{a} \pm 0.61$ |

Within each comparison, means with different superscripts are statistically significant at a 0.05 level of significance ($P < 0.05$). Small letters represent the interaction effects of both treatment and time. Capital letters represent the overall significance (main effect of treatment and main effect of time)

**Table 5** Mean ± standard deviation (SD) of physiological parameters at different time intervals

| Parameter | Time interval | Treatment | |
|---|---|---|---|
| | | G1 | G2 |
| Rectal temperature (°C) | Baseline | $39.30^{ab} \pm 0.17$ | $39.47^{a} \pm 0.50$ |
| | Premedication | $38.96^{abcd} \pm 0.29$ | $39.20^{abc} \pm 0.30$ |
| | Induction | $38.67^{abcde} \pm 0.12$ | $39.20^{abc} \pm 0.34$ |
| | 5 min | $38.43^{cdef} \pm 0.12$ | $39.10^{abc} \pm 0.20$ |
| | 10 min | $38.17^{defg} \pm 0.32$ | $38.90^{abcd} \pm 0.30$ |
| | 15 min | $37.96^{efg} \pm 0.42$ | $38.80^{abcd} \pm 0.30$ |
| | 20 min | $37.76^{fg} \pm 0.40$ | $38.53^{bcdef} \pm 0.58$ |
| | 30 min | $37.46^{g} \pm 0.51$ | $38.73^{abcde} \pm 0.51$ |
| | 60 min | $37.43^{g} \pm 0.61$ | $39.17^{abc} \pm 0.47$ |
| | 120 min | $37.46^{g} \pm 1.05$ | $39.33^{ab} \pm 0.15$ |
| Respiratory rate (breaths/min) | Baseline | $28.67^{a} \pm 11.71$ | $37.33^{a} \pm 3.05$ |
| | Premedication | $19.33^{a} \pm 4.61$ | $29.33^{a} \pm 7.02$ |
| | Induction | $40.67^{a} \pm 28.58$ | $47.0^{a} \pm 35.67$ |
| | 5 min | $41.33^{a} \pm 21.01$ | $49.33^{a} \pm 29.28$ |
| | 10 min | $40.0^{a} \pm 17.43$ | $37.33^{a} \pm 3.05$ |
| | 15 min | $38.67^{a} \pm 23.86$ | $43.33^{a} \pm 14.04$ |
| | 20 min | $38.0^{a} \pm 23.06$ | $42.33^{a} \pm 18.01$ |
| | 30 min | $40.0^{a} \pm 17.43$ | $36.0^{a} \pm 20.88$ |
| | 60 min | $26.67^{a} \pm 4.16$ | $52.33^{a} \pm 24.21$ |
| | 120 min | $15.33^{a} \pm 3.05$ | $40.33^{a} \pm 2.51$ |
| Heart rate (beats/min) | Baseline | $98.0^{abcde} \pm 7.21$ | $105.33^{abc} \pm 4.16$ |
| | Premedication | $72.67^{f} \pm 10.26$ | $114.0^{ab} \pm 12.49$ |
| | Induction | $76.67^{ef} \pm 15.27$ | $112.33^{ab} \pm 11.23$ |
| | 5 min | $72.0^{f} \pm 13.11$ | $99.33^{abcd} \pm 10.01$ |
| | 10 min | $79.33^{def} \pm 23.86$ | $92.67^{bcdef} \pm 9.45$ |
| | 15 min | $80.0^{def} \pm 10.0$ | $103.0^{abc} \pm 12.52$ |
| | 20 min | $74.0^{f} \pm 8.72$ | $92.67^{bcdef} \pm 11.01$ |
| | 30 min | $74.0^{f} \pm 8.72$ | $105.33^{abc} \pm 14.18$ |
| | 60 min | $77.33^{ef} \pm 7.02$ | $105.33^{abc} \pm 6.11$ |
| | 120 min | $85.33^{cdef} \pm 13.61$ | $116.36^{a} \pm 5.77$ |

Within each comparison, means with different superscripts are statistically significant at a 0.05 level of significance ($P < 0.05$). Small letters represent the interaction effects of both treatment and time. Capital letters represent the overall significance (main effect of treatment and main effect of time)

in group II showed fair induction and others good induction. The goats in group I rapidly assumed lateral recumbent position, and no forms of excitement were observed, whereas most goats in group II exhibited slight excitement, slightly prolonged induction, and presence of swallowing reflex. Recovery in group I was significantly longer than that in group II ($p < 0.01$). All goats in group I exhibited smooth recovery and transited from lateral recumbency to standing position without excitement, whereas most goats in group II exhibited poor recovery, prolonged struggling, premature attempts to stand, and ataxia (Table 6). In group I, a significantly depressed palpebral reflex was recorded after premedication up to 60 min, followed by moderately and mildly depressed at 75 and 90 min, respectively, whereas mild depression after premedication (diazepam), followed by excellent depression after induction until 45 min, was observed in group II (Fig. 1). Figure 2 reveals a mild depression in pedal reflex after DEX and diazepam premedication; however, excellent depression was observed after anesthesia induction in both groups up to the end of the anesthetic period. In group I, jaw relaxation was moderate in all animals after premedication with DEX and induction with ketamine, followed by excellent relaxation after maintenance with propofol, whereas moderate jaw relaxation after diazepam injection and jaw relaxed mildly after ketamine administration, followed

**Table 6** Mean ± standard deviation (SD) of clinical parameters between the two groups

| Parameter | Statistics | Group 1 | Group 2 | *P*-value |
|---|---|---|---|---|
| Onset of anesthesia (min) | Mean ± SD | $0.33^{b} \pm 0.08$ | $3.33^{a} \pm 1.53$ | 0.019* (T test) |
| | Minimum | 0.25 | 2 | |
| | Maximum | 0.42 | 5 | |
| Duration of anesthesia (min) | Mean ± SD | $66.67^{a} \pm 7.64$ | $37.0^{b} \pm 5.19$ | 0.005** (T test) |
| | Minimum | 60 | 31 | |
| | Maximum | 75 | 40 | |
| Total recovery period (min) | Mean ± SD | $98.33^{a} \pm 15.27$ | $47.0^{b} \pm 7.21$ | 0.006** (T test) |
| | Minimum | 85 | 41 | |
| | Maximum | 115 | 55 | |
| Quality of induction | Fair (n, %) | 0 (0%) | 2 (66.7%) | 0.001** |
| | Good (n, %) | 3 (100%) | 1 (33.3%) | |
| | *Chi-square test was applied* | | | |
| Quality of recovery | Poor (n, %) | 0 (0%) | 2 (66.7%) | 0.007** |
| | Fair (n, %) | 0 (0%) | 1 (33.3%) | |
| | Good (n, %) | 3 (100%) | 0 (0%) | |
| | *Chi-square test was applied* | | | |
| Onset of sedation (min) | Mean ± SD | $0.25 \pm 0.08^{b}$ | $2.0^{a} \pm 1.0$ | 0.026* (T test) |
| | Minimum | 0.17 | 1 | |
| | Maximum | 0.33 | 3 | |
| Duration of sedation (min) | Mean ± SD | $161.3^{a} \pm 43.3$ | $60.33^{b} \pm 7.57$ | 0.016* (T test) |
| | Minimum | 127 | 55 | |
| | Maximum | 210 | 69 | |

*Significant at 0.05 level ($P < 0.05$)

**Significant at 0.01 level ($P < 0.01$)

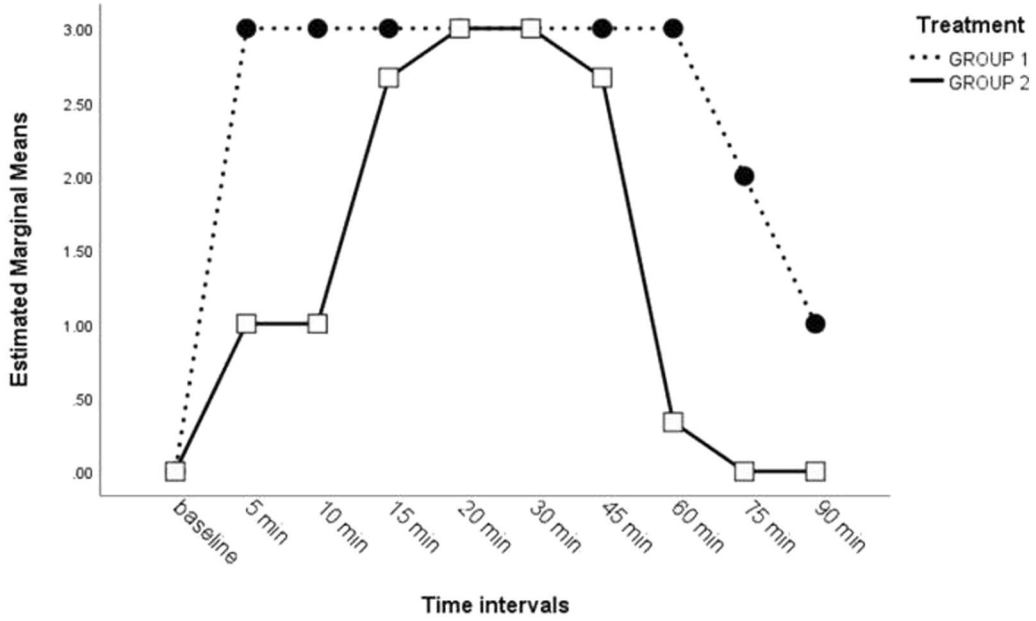


**Fig. 1** Line chart shows the means of palpebral reflex for the two groups at different time intervals

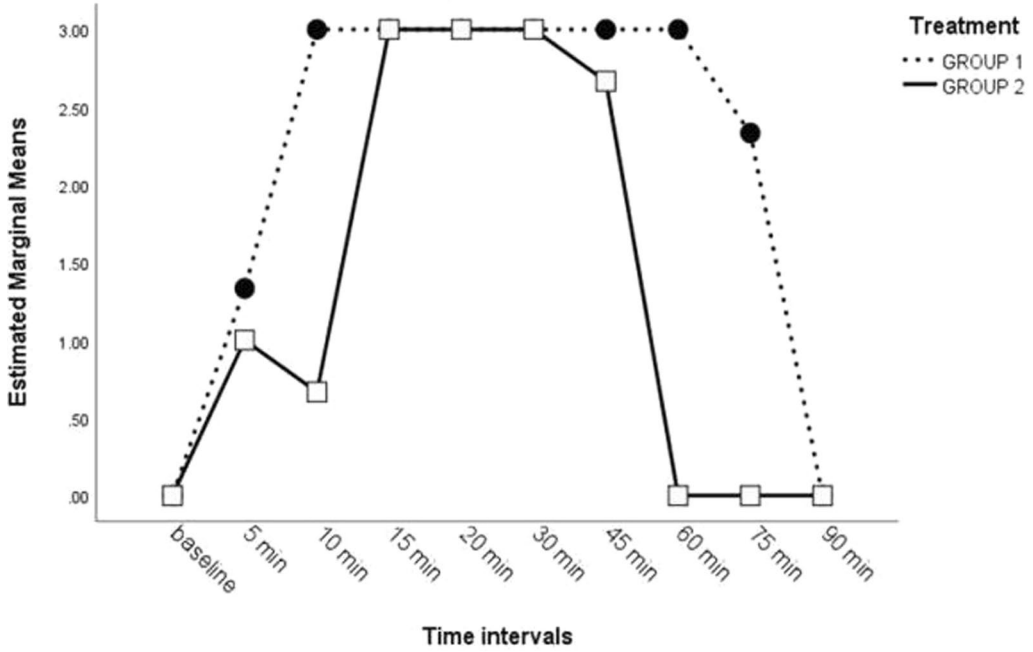


**Fig. 2** Line chart shows the means of pedal reflex for the two groups at different time intervals

by moderate to excellent relaxation after propofol injection, were noted in group II. Jaw relaxation was more significantly pronounced in group I at 45, 60, 75, and 90 min (Fig. 3). The sedation score in group I was significantly higher than that in group II at 10, 60, 90, and 120 min (Fig. 4).

## 4 Discussion

This study analyzed the effects of anesthesia with DEX–ketamine–propofol and diazepam–ketamine and propofol combinations on the physiological, hematobiochemical, and clinical parameters of goats. The goats in both groups showed mild respiratory acidosis. Acid–base

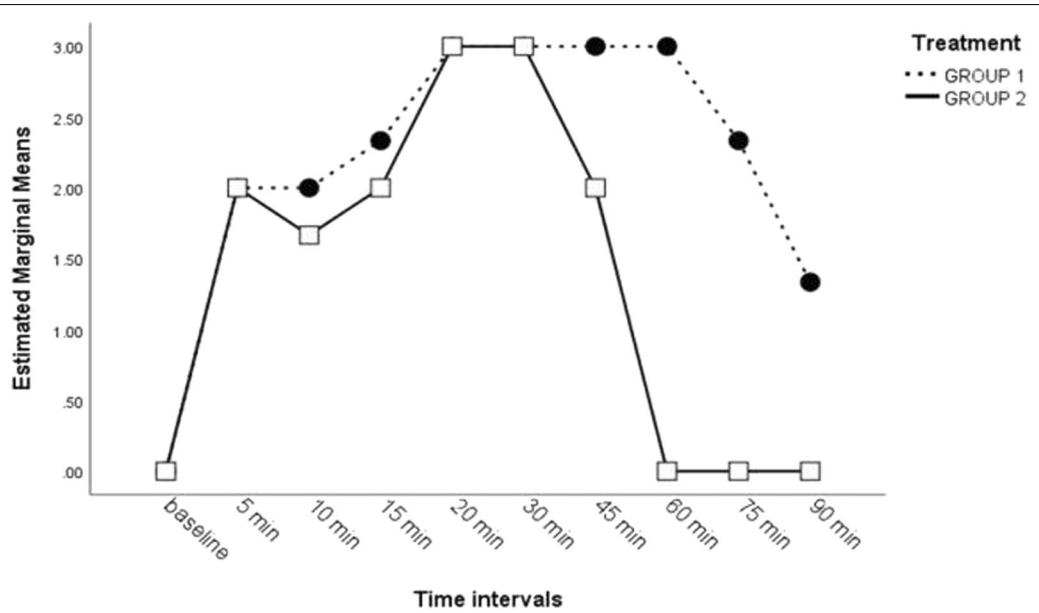


**Fig. 3** Line chart shows the means of jaw relaxation for the two groups at different time intervals

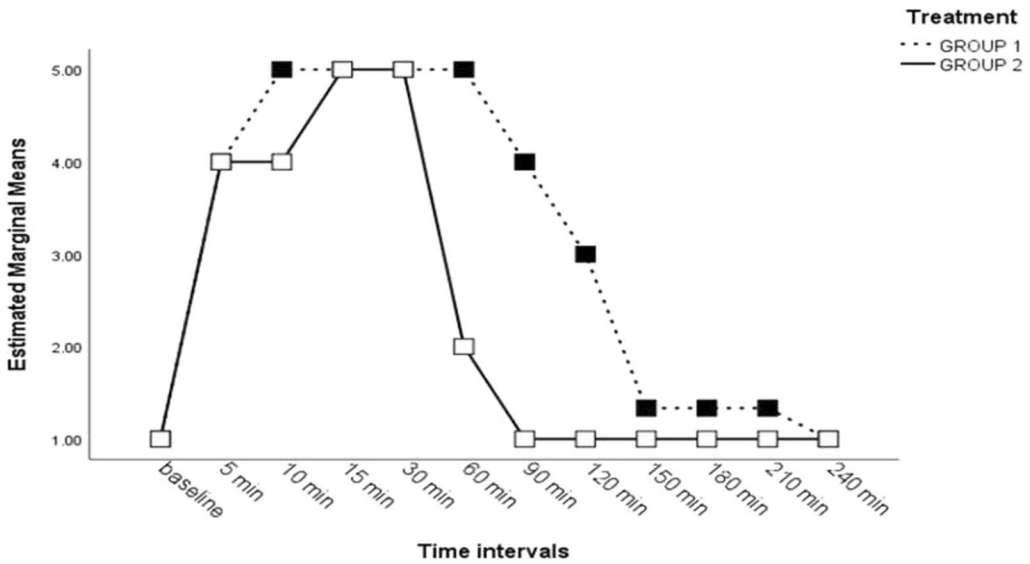


**Fig. 4** Line chart shows the means of the sedation score for the two groups at different time intervals

changes observed in this study reflected mild respiratory acidosis associated with induction and maintenance of anesthesia. A significant decrease in pH was detected after induction of anesthesia with tiletamine–zolazepam and propofol. However, these changes were not clinically relevant, and they were consistent with the effects after IV tiletamine–zolazepam administration to nonsedated dogs [13]. Respiratory acidosis was observed in goats anesthetized with propofol or isoflurane anesthesia maintenance combined with a fentanyl–lidocaine–ketamine constant-rate infusion due to an increase in $pCO_2$ [14]. In a study performed in dogs, it was determined that propofol administration for the induction of anesthesia did not alter pH, $PaCO_2$, and $HCO_3$ levels in comparison with the initial values despite increased arterial oxygen saturation, arterial partial pressure of oxygen, and $PvO_2$ levels [15]. An increased value of plasma glucose was observed in both groups, of which group I showed a significant increase compared with that at baseline; this result may be due to decreased membrane transport of glucose, decreased glucose utilization, impaired insulin activity, and increased blood concentration of adrenocortical hormones. Ketamine has been reported to cause sympathetic stimulation leading to the release of catecholamines and increased glucose concentration in plasma. It was reported that there was a nonsignificant increase in the glucose concentration after butorphanol–DEX–ketamine administration [16]. It was found that the increase in the glucose level occurred after the administration of diazepam and/or xylazine dosage injection that started within 20 min of diazepam and/or xylazine dosage injection in mice [17]. BUN and serum creatinine levels did not significantly fluctuate until the end of the observation period in both groups, indicating the absence of renal insufficiency. This finding is consistent with those of Saini et al. and GH et al. [6, 18]. Nonsignificant fluctuations were noted in ALT/AST levels in group I, resembling the fluctuations found after DEX and ketamine administration in dogs [18]. A significant increase in ALT was observed in group II at 30 and 60 min; this increase may be due to the increased permeability that may permit enzyme leakage from the cells with intact membrane. When there is stress or any damage to the liver cells, the enzyme escapes into the blood, thereby increasing the ALT enzymatic activity [19]. The reduction in RBC, PCV, and Hb levels in this study may be credited to the merging of blood cells in the spleen, caused by the adrenolytic property of α2-adrenoceptor drugs and dissociative anesthetic drugs. However, it was recorded that the reduction in these parameters was ephemeral and refunded near the baseline values at 24-h intervals. This result resembled that found after ketamine–DEX–sevoflurane anesthesia in dogs [20] and also reported during the clinical evaluation of IV propofol alone or in combination with diazepam, ketamine, and thiopental sodium to induce general anesthesia in dogs [21]. The increase in the cortisol level was consistent with the findings of Bisht et al. [20] who recorded an increase in the cortisol level in dogs administered with DEX with ketamine. Another study revealed a consistent response of the corticoadrenal gland with respect to glucocorticoid secretion after the induction of anesthesia with ketamine and propofol.

However, serum glucocorticoid concentrations did not significantly change after DEX–propofol anesthesia. Some studies have reported that glucocorticoid levels increase after propofol anesthesia in rats. Recent results suggest that propofol has a stimulatory effect on serum cortisol concentration in rabbits [22].

The decrease in RT may be due to the decreased muscular activities and effect of α2-adrenoceptor agonism by DEX, which is consistent with the results reported by Verma et al. [23]. The decrease in RT has been previously attributed to the depression of the hypothalamic thermoregulatory center, which is consistent with the results of anesthesia with diazepam, lidocaine, and their combination in Red Sokoto goats [24]. The current study revealed no significant influence on RR in both groups, suggesting a minimal effect of diazepam and DEX on RR; such finding is consistent with that obtained by Wu et al. [25] who found no significant effect on RR during the combination of DEX with midazolam nasal drops in children. Conversely, a previous study revealed that respiratory depression was positively correlated with the dose of midazolam, and it was reported that DEX could provide appropriate sedation for children without affecting hemodynamics or causing respiratory depression. A previous study performed on cats to evaluate the sedative effects of DEX, DEX–pethidine, and DEX–butorphanol revealed that the RR was significantly decreased although remained similar to the baseline in another study [26]. The decrease in HR in group I might be due to the effect of DEX since it is believed to produce bradycardia in animals. DEX initially causes vasoconstriction in the pulmonary and systemic circulations, subsequently causing a decrease in HR and cardiac output [27]. Group I showed more rapid onset and longer duration of anesthesia and sedation with higher sedation scores than group II. These results are consistent with that reported by Azizkhani et al. [28] who reported that DEX was superior to midazolam owing to higher sedation, lower emergence delirium, and faster starting effect of sedation. The faster onset of anesthesia in group I may be due to the effect of DEX, which produced an adequate degree of sedation preceding induction. DEX has a rapid onset of action owing to its lipophilic properties. Moreover, it was reported that potent sedation enabling minor clinical procedures in dogs was achieved with intramuscular administration of DEX at 10 μg/kg. Additionally, it was reported that butorphanol and DEX combination achieves high sedation in dogs [27]. In a study performed on dogs, the induction time in the group anesthetized with etomidate–DEX was significantly less than that anesthetized with etomidate–midazolam ($P<0.05$). In our study, the quality of anesthesia was excellent in DEX-premedicated animals than diazepam-premedicated ones. Moreover, the duration of anesthesia in group I was longer than that in group II, which is consistent with the results obtained during the comparison between DEX–etomidate and midazolam–etomidate anesthesia in dogs, wherein the anesthesia duration was $48.37 \pm 0.81$ min in the midazolam-premedicated group and $77.25 \pm 1.84$ min in the DEX-premedicated group. The quality of anesthesia was excellent in the DEX-premedicated group [29].

The quality of induction and recovery in group I, which was premedicated with DEX, was better than that in group II, which was premedicated with diazepam. This study revealed that the DEX-premedicated group had smooth and excellent induction and recovery without excitement of any animals. The results were similar to those obtained during the combination of DEX and ketamine in monkeys, which resulted in good quality of anesthesia accompanied by smooth induction and recovery [30]. However, in diazepam-premedicated animals, some exhibited ataxia, excitement, and struggling with a shorter recovery period, which is consistent with the results reported by Shaaban et al. [21] who recorded that convulsions and urination were observed during recovery in dogs administered with propofol and diazepam. The recovery period in group I premedicated with DEX was higher than that in group II premedicated with diazepam. The results are consistent with that reported by Bisht et al. [20] who suggested that standing and sternal recumbency times increased and decreased, respectively, according to the DEX dosage. The sedative effect of DEX led to longer anesthesia and recovery time. Furthermore, Kamble et al. [29] reported that the standing time and complete recovery period were significantly longer in DEX-premedicated animals than in midazolam-premedicated ones in total IV anesthesia of etomidate in dogs ($p<0.05$).

Good muscle relaxation was recorded in detomidine–propofol, midazolam–propofol, and midazolam–ketamine combinations, whereas excellent muscle relaxation was noted with detomidine–midazolam–ketamine and propofol combinations in goats [3]. Saini et al. [31] also reported that DEX produced excellent analgesia and muscle relaxation, making it a suitable anesthetic combination for surgical procedures with longer duration in dogs. Mild pedal reflex depression was noticed after DEX premedication, followed by excellent depression after induction of anesthesia with ketamine or propofol [32]. In the present study, complete abolition of palpebral reflexes after DEX administration was noted, which was consistent with the findings of Swamy [33] who revealed that the reflexes were absent during general anesthesia with romifidine–guaifenesin–ketamine and DEX–guaifenesin–ketamine combinations in cattle at 30 and 60 min. At 2 h, all the reflexes were regained in

both groups. It was reported that buffaloes showed complete abolition of palpebral reflexes and mild response to corneal reflex after DEX and fentanyl premedication, which was completely abolished after induction of anesthesia with thiopentone and isoflurane. In group II, an adequate degree of muscle relaxation was observed after the maintenance period, with mild depression in palpebral and pedal reflexes after diazepam injection, which became moderately to completely depressed after the induction and maintenance of anesthesia. These findings are consistent with that reported by Bodh et al. [34] who reported that a better degree of muscle relaxation was achieved by midazolam–butorphanol combination, which was attributed to the synergistic effect of both drugs. Mild palpebral and corneal reflex depression was seen after premedication. Complete/moderate palpebral and corneal reflex abolition after anesthetic induction and throughout the maintenance period was noted.

## 5 Conclusions

In TIVA, premedication with DEX produces pronounced hypothermia and bradycardia compared with premedication with diazepam. Both treatments are associated with hemodynamic stability. Premedication with DEX produces excellent quality of anesthesia and muscle relaxation with prolonged duration of anesthesia, analgesia, and sedation; therefore, it is more suitable than premedication with diazepam for major surgical procedures with long duration in goats.

#### Abbreviations

RR: Respiratory rate; HR: Heart rate; RT: Rectal temperature; Hb: Hemoglobin; PCV: Packed cell volume; ALT: Alanine aminotransferase; RBC: Red blood cell count; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; TIVA: Total intravenous anesthesia; DEX: Dexmedetomidine; $PO_2$: Partial pressure of oxygen; $PCO_2$: Partial pressure of carbon dioxide; $SO_2$: Oxygen saturation; $HCO_3$: Bicarbonate; $SaO_2$: Arterial oxygen saturation; $PaO_2$: Arterial partial pressure of oxygen; SD: Standard deviation.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43088-022-00232-0.

**Additional file 1: Table S1**. Normal range values for different physiological and hematobiochemical parameters assessed in this study.

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#### Author contributions

SEH performed the study and wrote the manuscript. GR, MZF, UH, and SEH designed the work and reviewed the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

By corresponding author.

## Declarations

#### Ethics approval and consent to participate

The animal protocol was approved by the BSU-IACUC reviewers under approval number 021–173.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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#### References

1. Verma KK, Tiwari SK, Dewangan R, Sharda R (2018) Effect on haematological and biochemical profiles following administration of ketamine alone and in combination with dexmedetomidine or butorphanol in atropinized dogs. Int J Curr Microbiol Appl Sci 7(6):2568–2577. https://doi.org/10.20546/ijcmas.2018.706.303
2. Akter MA, Orchy KAH, Khan MMR, Hasan M, Hasan M, Alam MM (2020) Clinical Evaluation of general Anaesthesia using ketamine hydrochloride with and without Diazepam in Sheep. Arch Vet Sci Med 3(3):63–75. https://doi.org/10.26502/avsm.016
3. Asif M, Khan MA, Akbar H, Omer MO (2021) effects of detomidine and midazolam administered alone or combined, on induction dose and quality of propofol and ketamine anesthesia in goats. JAPS J Anim Plant Sci. https://doi.org/10.36899/JAPS.2021.2.0233
4. Pan SY, Liu G, Lin JH, Jin YP (2021) Efficacy and safety of dexmedetomidine premedication in balanced anesthesia: a systematic review and meta-analysis in dogs. Animals 11(11):3254. https://doi.org/10.3390/ani11113254
5. Lervik A, Toverud SF, Krontveit R, Haga HA (2020) A comparison of respiratory function in pigs anaesthetised by propofol or alfaxalone in combination with dexmedetomidine and ketamine. Acta Vet Scand 62(1):1–9. https://doi.org/10.1186/s13028-020-0512-y
6. GHR, Mms, M Halfaya F, (2017) Comparison of quality of anesthetic effect between intramuscularly administered ketamine, intravenously administered ketamine and intravenously administered propofol in diazepam premedicated goats. J Vet Med Res 24(2):247–256
7. Udegbunam RI, Ugwu AU, Onuba AC, Okereke NH, Udegbunam SO (2019) Effects of sub-anaesthetic (low) dose ketamine infusion on intra-operative and postoperative pain in goats anaesthetized with diazepam-ketamine prior to rumenotomy. Sokoto J Vet Sci 17(1):19–26. https://doi.org/10.4314/sokjvs.v17i1.3
8. Benjamin MM (1978) Outline of veterinary clinical pathology, 2nd edn. Iowa State University Press, Iowa, pp 35–105
9. Dacie JV, Lewis SM (1984) Practical haematology, 6th edn. Churchill Livingston, Edinburgh, pp 24–36
10. Jain NC (1986) Schalm's veterinary haematology, 4th edn. Lea Febiger, Philadelphia, p 1221
11. Chaney AL, Marbach EP (1962) Modified reagents for determination of urea and ammonia. Clin Chem 8(2):130–132. https://doi.org/10.1093/clinchem/8.2.130
12. Breuer J (1996) Report on the symposium" Drug effects in Clinical Chemistry Methods". In European journal of clinical chemistry and clinical biochemistry: journal of the Forum of European Clinical Chemistry Societies 34(4):385–386

13. Hampton CE, Riebold TW, LeBlanc NL, Scollan KF, Mandsager RE, Sisson DD (2019) Effects of intravenous administration of tiletamine-zolazepam, alfaxalone, ketamine-diazepam, and propofol for induction of anesthesia on cardiorespiratory and metabolic variables in healthy dogs before and during anesthesia maintained with isoflurane. Am J Vet Res 80(1):33–44. https://doi.org/10.2460/ajvr.80.1.33
14. Velázquez-Delgado PI, Gutierrez-Blanco E, Torres-Acosta FDJ, Ortega-Pacheco A, Aguilar-Caballero AJ, Dzikiti BT (2021) Comparison of propofol or isoflurane anesthesia maintenance, combined with a fentanyl–lidocaine–ketamine constant-rate infusion in goats undergoing abomasotomy. Animals 11(2):492. https://doi.org/10.3390/ani11020492
15. Gokalp E, Gurgoze S, Altan S (2020) Effects of xylazine-ketamine, xylazine-propofol and xylazineketamine-propofol administration on free radical generation and blood gases in sheep. Indian J Anim Res 54(2):149–154
16. Arya N, Shukla BP, Jain R, Rajput N, Parihar A (2021) Haemato-biochemical evaluation of glycopyrrolate, dexmedetomidine, butorphanol/buprenorphine as Preanesthetic with ketamine dissociative anesthetic in canines. Pharma Innov 10(6):803–807
17. Mohammed AA, Al-Hozab A, Alshaheen T (2018) Effects of diazepam and xylazine on changes of blood oxygen and glucose levels in mice. Adv Anim Vet Sci 6(3):121–127. https://doi.org/10.17582/journal.aavs/2018/6.3.121.127
18. Saini R, Jadon NS, Kandpal M, Kumar A (2019) Clinicophysiological and haematobiochemical effects of dexmedetomidine as preanesthetic in combination with thiopental sodium and ketamine in dogs. Pharma Innovation 8(7):12–17
19. Yakubu AS, Usman IB, Kabir H, Abubakar AA, Bello A, Oviawe EI, Abubakar N, Bodinga HA (2020) Effects of lignocaine-diazepam combination in lumbo-sacral epidural anaesthetized dogs undergoing caudectomy. J Adv Biol Biotechnol 23(2):11–18. https://doi.org/10.9734/jabb/2020/v23i230139
20. Bisht DS, Jadon NS, Bodh D, Kandpal M (2018) Clinicophysiological and haematobiochemical evaluation of dexmedetomidine-ketamine-sevoflurane anaesthesia in dogs. Indian J Vet Surg 39(2):121–125
21. Shaaban MF, Kassem MM, EL Kammar MH, Korittum SA (2018) Clinical evaluation of intravenous propofol alone or in combination with Diazepam, Ketamine Hcl and thiopental sodium to induce general anaesthesia in dogs. Alex J Vet Sci 57(1):106–114. https://doi.org/10.5455/ajvs.290272
22. González-Gil A, Picazo R, de Bruyn P, Illera JC (2018) Corticoadrenal and cardiorespiratory responses to administration of propofol combined with dexmedetomidine or ketamine in rabbits. J Am Assoc Lab Anim Sci 57(3):278–281
23. Verma A, Sooryadas S, Dinesh PT, Chandy G, Caulkett N (2020) Continuous rate infusion anaesthesia with dexmedetomidine-midazolam-ketamine-lignocaine in dogs. Indian J Vet Surg 41(2):104–106
24. Yakubu AS, Pilau NN, Abubakar AA, Mshelia PC, Bodinga HA, Abubakar N, Ahmad US (2020) Effects of Diazepam, lidocaine and their combination on clinical parameters, haematological indices and electrolytes profile in the Red Sokoto Goat. Niger J Anim Sci 22(1):201–207
25. Wu ZF, He L, Lai Y, Li SJ, Zhang YP (2020) Observation of the sedative effect of dexmedetomidine combined with midazolam Nasal Drops before a pediatric craniocerebral MRI. J Craniofac Surg 31(6):1796–1799. https://doi.org/10.1097/scs.0000000000006657
26. Varkoulis K, Pavlidou K, Savvas I (2020) The effect of dexmedetomidine combined with butorphanol on cardiovascular and respiratory system in cats. Hellenic J Companion Anim Med 9(1):86–94
27 Bayan H, Sarma KK, Rao GD, Kalita D, Dutta D, Phukan A (2020) Propofol and ketamine CRI in dexmedetomidine and butorphanol premedicated dogs. Pharma Innov 9(3):334–337. https://doi.org/10.22271/tpi.2020.v9.i3g.4493
28. Azizkhani R, Heydari F, Ghazavi M, Riahinezhad M, Habibzadeh M, Bigdeli A, Golshani K, Majidinejad S, Mohammadbeigi A (2020) Comparing sedative effect of dexmedetomidine versus midazolam for sedation of children while undergoing computerized tomography imaging. J Pediatr Neurosci 15(3):245. https://doi.org/10.4103/jpn.jpn_107_19
29. Kamble M, Sharda R, Dewangan R, Tiwari SK, Ali SL, Jolhe DK, Singh M, Gumasta P, Sonkusale PM, Kalim MO (2021) Comparative evaluation of clinico-physiological effect of total intravenous anaesthesia of etomidate in midazolam and dexmedetomidine premedication in dogs. Pharma Innov J 10(11S):15–20
30. Chagas JAB, Santos LCP, Silva Filho JR, Bondan C (2018) Anaesthetic and cardiorespiratory effects of ketamine plus dexmedetomidine for chemical restraint in black capuchin monkeys (*Sapajus nigritus*). N Z Vet J 66(2):79–84. https://doi.org/10.1080/00480169.2017.1403975
31. Saini R, Jadon NS, Kandpal M, Bodh D (2017) Studies on the effects of thiopental sodium with and without dexmedetomidine in dogs. Indian J Vet Surg 38(1):44–46
32. Kumar R, Kinjavdekar P, Amarpal HA, Pawde AM, Singh J, Khattri S (2018) Comparative evaluation of propofol and ketamine total intravenous anaesthesia (TIVA) with dexmedetomidine and butorphanol in goats. Indian J Anim Sci 88(6):667–671
33. Swamy K (2021) Clinical and physiological evaluation of induction combinations romifidine guaifenesin ketamine and dexmedetomidine guaifenesin ketamine under isoflurane anesthesia in cattle. Pharma Innov J 10(11S):1990–1992
34. Bodh D, Singh K, Mohindroo J, Gopinathan A, Mahajan SK, Saini NS (2015) Evaluation of midazolam and midazolam-butorphanol premedications for general anaesthesia in buffaloes (*Bubalus bubalis*). Indian J Vet Surg 36(2):77–81


## Publisher's Note