CARDIOPULMONARY, BIOCHEMICAL, AND HAEMATOLOGICAL CHANGES AFTER DETOMIDINE-MIDAZOLAM-KETAMINE ANAESTHESIA IN CALVES

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Abstract

The aim of the study was to investigate the suitability of detomidine-midazolam-ketamine combination for umbilical surgery in calves. Fifteen calves subjected to umbilical surgery received detomidine (100 µg/kg b.w.), midazolam (0.5 mg/kg b.w.), and ketamine (10 mg/kg b.w.) intravenously (iv), as a mixture of the drugs. Rectal temperature, heart rate, pulse, and respiratory rate were recorded before drug administration and at 5, 10, 15, 30, and 45 min after anaesthesia. Haematological and biochemical parameters were detected before drug administration, 15, 30, 45, and 60 min after drug injection and 24 h after anaesthesia. The combination of the compounds resulted in anaesthesia lasting about 45 min and a satisfactory immobilisation for umbilical surgery, although some hypoxaemia and respiratory acidosis occurred. The body temperature of the calves decreased significantly (P<0.05) during the anaesthesia from 38.5°C to 37.9°C. Haemoglobin, PCV, and RBC decreased significantly (P<0.05) for a short time. The values for plasma glucose, creatinine, and ALT increased significantly (P<0.05). However, they returned to the baseline at 24 h. Muscle relaxation was good and no complications were encountered.

Key words: calves, surgery, detomidine, ketamine, midazolam.

General anaesthesia is required in calves for complex surgical or diagnostic procedures. Inhalation anaesthesia requires specific equipment and may only be possible under hospital conditions. It is rarely feasible for the use in the field. The adverse effects of atmospheric pollution and low-level personnel exposure to volatile anaesthetics must also be considered.

α2-agonists are effective sedatives in calves; xylazine is currently used to provide sedation and immobilisation, including recumbency and light planes of general anaesthesia (4). However, it causes hypoxaemia and hypercapnia in calves (21, 24) and may induce acute pulmonary oedema in sheep (27). Various injectable anaesthetic techniques can be used for calves under field conditions. Thiobarbiturates alone or in combination with guaiphenesin (GGE) can be used for the induction and maintenance of anaesthesia (25). Ketamine is commonly used in calves alone or combined with xylazine (23, 29, 30), or medetomidine (22). The combination of medetomidine and ketamine produced satisfactory immobilisation for umbilical surgery, although some hypoxaemia and respiratory acidosis occurred. Muscle relaxation was good and no complications were encountered. Tiletamine, another cyclohexanone derivative, and zolazepam (a benzodiazepine) may also be used. This combination has been investigated for the use with and without xylazine (11, 26). Propofol, a non-barbiturate, non-steroidal hypnotic agent produces short-time anaesthesia in most species. Economic and licensing factors limit its use in farm animals.

Detomidine alone at the dose rate of 100 µg/kg produced only mild sedation and analgesia in buffalo calves (17). The addition of diazepam and ketamine to detomidine produced anaesthesia of a short duration (15 min) and prolonged sedation and analgesia. The combination of detomidine- diazepam-ketamine may be used safely in buffalo calves to induce a transitory anaesthesia or chemical immobilisation for clinical examination (17).

The purpose of the present study was to investigate the suitability of detomidine-midazolame-ketamine combination for umbilical surgery in calves.

Material and Methods

The study was approved by the University of Adnan Menderes Institutional Animal Care and Use Committee.

Appropriate doses of detomidine (Domosedan; Orion Corporation Farmos, Finland), ketamine (Alfamyne; Egevet, Turkey), and midazolame
(Demizolam; Dem, Turkey) were mixed in a syringe and the mixture was used to induce anaesthesia in 15 Holstein calves (7 males and 8 females), weighing 40-120 kg and 5 to 90 d of age, with umbilical problems (hernia, abscess, omphalophlebitis, urachitis). They were not fed in the morning of the procedure day. All the calves were given intravenously 100 pg/kg b.w. of detomidine, 10 mg/kg b.w. of ketamine, and 0.5 mg/kg of midazolame. The calves were operated on dorsal recumbency. Lidocaine (Carbocain; Astra, Sweden) in a dose of 20 mg/mL was used subcutaneously at the incision site as a local anaesthetic.

The following variables were measured before and 5, 10, 15, 30, and 45 min after drug injection: heart rate (HR, beats/per min), respiratory rate (RR, breaths/per min), rectal temperature (CT), sodium (Na+), potassium (K+), ionised calcium (iCa++), arterial pH (pHa), arterial oxygen tension (paO2), arterial carbon dioxide tension (paCO2), bicarbonate concentration (HCO3), and base excess (BE). Respiratory rate was determined by a direct observation. Arterial blood samples were collected into heparinised syringes for the measurement of electrolytes and blood gas values. Air was removed from the blood gas syringe, and the sample was immediately analysed using an automated blood gas analyser (Model ITC Irma Tripoint, Blood analysis System, ITC, USA), which corrected the reported values for body temperature to 41°C. The values of total protein, ALT, AST, creatinine, urea, and glucose were determined by Microlab 200 (Merck) using commercially available kits (Biomedical Systems, Spain). The analyses were carried out according to the manufacturer’s instructions. To determine the number of erythrocytes (RBC) and leukocytes (WBC), packed cell volume (PCV), and haemoglobin (Hb) concentration, blood was collected into heparinised tubes at baseline and 15, 30, 45, and 60 min after induction of anaesthesia with detomidine/midazolam/ketamine and 24 h after the anaesthesia and analysed by a automatic cell counter (Abacus Junior Vet, Interpet, Turkey). The animals were observed continuously during the recovery period until they were standing.

The data were analysed with ‘Statgraphics’ statistical graphics programme using paired and unpaired Student’s t-tests. Minimum statistical significance was taken as P<0.05.

Results

The calves showed the first signs of sedation (sunken head and reduced awareness) 0.7±0.3 min after the administration of the combination of the drugs. They lay down, usually first to sternal recumbency, 1.1 ± 0.8 min after the injection and were deeply sedated in lateral recumbency after 1.7 ± 0.57 min. The combination of detomidine, midazolam, and ketamine resulted in the anaesthesia lasting about 45 min. Heart and respiratory rates, paO2, paCO2, pH, and electrolytes before and after administration of medetomidine are shown in Table 1.

There was a statistically significant decrease (P<0.05) in the mean heart rate, arterial pH, and paO2 and an increase (P<0.05) in paCO2 within 5 min of the injection. Respiratory rate increased significantly (P<0.05) with time, whereas base excess had a slight tendency to decrease. The body temperature decreased significantly (P<0.05) during the anaesthesia from 38.5 ±0.3°C to 37.9±0.4. The blood sodium, kalium, and ionised calcium decreased with time during the whole period of anaesthesia.

### Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0 (baseline)</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>30</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>87±13.6</td>
<td>72.5±6.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77.7±7.7</td>
<td>78.0±11.1</td>
<td>78.9±6.3</td>
<td>73.1±5.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>22.7±12.2</td>
<td>37.5±11.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36.2±12.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43.1±10.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.8±12.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.1±13.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T(C)</td>
<td>38.5±0.3</td>
<td>38.4±0.3</td>
<td>38.3±0.2</td>
<td>38.3±0.5</td>
<td>38.3±0.3</td>
<td>37.9±0.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.43±0.01</td>
<td>7.38±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.35±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.33±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.31±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.30±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>paCO2 (mmHg)</td>
<td>48±5</td>
<td>54.5±3.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55±0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58±2.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61±0.24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>paO2 (mmHg)</td>
<td>93±5.1</td>
<td>78.5±3.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72.6±6.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71.7±11.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67.7±7.30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66.8±6.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HCO3 (mEq/L)</td>
<td>29.8±2.3</td>
<td>29.5±2.8</td>
<td>29.4±3.0</td>
<td>28.8±1.7</td>
<td>27.7±2.8</td>
<td>27.2±4.1</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>6.6±2.5</td>
<td>4.8±3.7</td>
<td>3.6±2.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.7±1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1.3±3.30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-2.8±4.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Na+(mmol/L)</td>
<td>138±2.3</td>
<td>136±3.3</td>
<td>132±2.1</td>
<td>134±4.3</td>
<td>132±2.3</td>
<td>132±4.3</td>
</tr>
<tr>
<td>K+(mmol/L)</td>
<td>4.40±1.3</td>
<td>4.2±1.1</td>
<td>3.97±0.9</td>
<td>4.27±1.2</td>
<td>3.8±0.9</td>
<td>3.9±1.3</td>
</tr>
<tr>
<td>iCa++(mmol/L)</td>
<td>1.32±0.3</td>
<td>1.29±0.2</td>
<td>1.26±0.4</td>
<td>1.27±0.6</td>
<td>1.23±0.3</td>
<td>1.20±0.2</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SE.  
<sup>a</sup> Mean value differs significantly (P<0.05) from baseline value; BE= base excess
The haematological and biochemical variables are shown in Table 2. The ALT and ALP increased significantly (P<0.05) with time during the anaesthesia and returned to the baseline at 24 h. The values of serum concentrations of creatinine, urea nitrogen, and glucose showed a significant (P<0.05) increase during post-injection period. Haemoglobin, PCV, and RBC decreased significantly (P<0.05) for a short time in all animals after the injection of the compounds. The values for PCV and Hb; however, it returned to the baseline and the values for WBC showed a non-significant increase at 24 h.

**Discussion**

According to Blaze et al. (2) after administration of medetomidine and ketamine to the calves, paCO₂ increased and heart rate, paO₂, and pH decreased, as has been reported during xylazine/ketamine narcosis. Five minutes after the first medetomidine/ketamine injection, all the calves were acidic. The lowest individual arterial pH measured in this study was 7.3, which was no lower than the lowest pH recorded by the mentioned authors. The combination of detomidine, midazolam, and ketamine resulted in anaesthesia lasting about 45 min. The duration of anaesthesia induced by xylazine/ketamine (0.2 mg/kg b.w. and 5 mg/kg b.w. or 10 mg/kg b.w., respectively) was approximately 23 min in calves older than 10 weeks of age (29).

In our experience, the duration of the sedation and analgesia induced by detomidine/midazolam/ketamine is enough for students to perform umbilical herniotomy. In the present study, local analgesic solution was used only in the subcutaneous tissues to reduce the need for another dose of detomidine/midazolam/ketamine while the skin was sutured, and only for calves operated in dorsal recumbency. The calves did not react when the muscular layers or peritoneum were manipulated. The potency of detomidine made it possible to reduce the dose of ketamine to 0.5 mg/kg b.w., which is only 10% of the dose used in combination with xylazine (2, 29).

Rectal temperature decreased in this study. A decrease in RT was recorded following systemic administration of α₂-adrenoceptor agonists (16), which was attributed to the depression of the hypothalamic thermoregulatory centre (12). The decrease in RT was also probably the result of a reduced basal metabolic rate (BMR) and muscle activity, and depression of thermoregulatory centre (18). Hypothermia was also observed after administration of medetomidine in goats (13).

Haemoglobin, PCV, and RBC decreased for a short time in all the groups after the administration of detomidine, midazolam, and ketamine. However, the values for PCV and Hb returned to the base line and the values for WBC showed a non-significant increase at 24 h. Pooling of circulating blood cells in the spleen and other reservoirs secondary to decreased sympathetic activity could be the reason for a decrease in Hb, PCV, and WBC (8, 17). The decrease in PCV and Hb during the period of anaesthesia or sedation might be attributed to the shifting of fluid from extravascular compartment to intravascular compartment in order to maintain normal cardiac output in the animals (28).

The values for plasma glucose increased in animals of all the groups. Hyperglycaemic effects of α₂-adrenoceptor agonists are well known. There have been many investigations into the hyperglycaemic effects of xylazine (5, 6) and medetomidine (3). The hyperglycaemic effect might be to the result of α₂-adrenergic receptor inhibition of insulin release by the stimulation of α₂-adrenoceptors in the pancreatic β cells (1) and to an increased glucose production in the liver (6).

A significant increase in plasma creatinine was recorded in all the groups. The values returned to baseline in 24 h in all animals. The increase in plasma creatinine might be attributed to the temporary inhibitory effect of these drugs on the renal blood flow, which in turn might have caused a rise in plasma creatinine values. However, it is difficult to ascribe this to possible renal damage, because all the reported values were within normal physiological limits (7). Parenteral administration of xylazine was also reported to cause a

### Table 2

<table>
<thead>
<tr>
<th>Time</th>
<th>0 (baseline)</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>26.8±3.6</td>
<td>32.5±3.2</td>
<td>40.7±4.2</td>
<td>42.0±1.1</td>
<td>43.89±0.3</td>
<td>23.1±2.2</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>288.5±12.3</td>
<td>331.1±3.8</td>
<td>340.3±0.6</td>
<td>360.9±1.5</td>
<td>385±0.2</td>
<td>300.5±0.2</td>
</tr>
<tr>
<td>TP (mg/dL)</td>
<td>6.8±0.8</td>
<td>6.3±0.8</td>
<td>6.5±0.8</td>
<td>6.2±0.8</td>
<td>6.0±0.8</td>
<td>6.9±0.8</td>
</tr>
<tr>
<td>Ure (mg/dL)</td>
<td>24.6±1.6</td>
<td>31.2±2.7</td>
<td>39.9±0.3</td>
<td>32.0±2.1</td>
<td>36.1±5.6</td>
<td>28.5±2.6</td>
</tr>
<tr>
<td>Creatinin (mg/dL)</td>
<td>1.23±0.07</td>
<td>1.45±0.03</td>
<td>1.47±0.03</td>
<td>1.61±0.1</td>
<td>1.68±0.02</td>
<td>1.26±0.01</td>
</tr>
<tr>
<td>Glucose (mEq/L)</td>
<td>64.3±1.9</td>
<td>80.5±2.8</td>
<td>79.4±3.1</td>
<td>81.8±2.7</td>
<td>83.7±2.8</td>
<td>61.3±3.4</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.88±0.8</td>
<td>10.82±1.1</td>
<td>9.95±0.8</td>
<td>9.76±1.2</td>
<td>9.82±1.4</td>
<td>11.2±1.6</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>28.8±1.9</td>
<td>27.5±2.9</td>
<td>26.6±1.1</td>
<td>26.2±2.1</td>
<td>26.4±2.5</td>
<td>30.5±1.9</td>
</tr>
<tr>
<td>WBC (×10⁹/L)</td>
<td>16.6±0.2</td>
<td>13.3±0.3</td>
<td>12.2±0.8</td>
<td>12.6±0.5</td>
<td>11.8±0.4</td>
<td>18.6±0.8</td>
</tr>
<tr>
<td>RBC (×10⁶/L)</td>
<td>6.92±0.4</td>
<td>6.32±0.3</td>
<td>5.80±0.2</td>
<td>5.66±0.3</td>
<td>5.75±0.2</td>
<td>7.01±0.4</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SE.

*a Mean value differs significantly (P<0.05)
rise in creatinine level in buffaloes (14). Plasma urea nitrogen showed a significant increase in all the groups during post-injection period. This might be attributed to a temporary inhibitory effect of the drug on the renal blood flow, which in turn might have caused a rise in BUN (9). In addition, increased hepatic urea production from amino acid degradation could account for the observed increase in BUN values as was recorded by Eichner et al. (5). Similar changes in BUN were also reported after administration of detomidine in goats (10) and after xylazin-diazepam administration in horses (8). However, no change in BUN was observed after xylazine injection in goats (10).

The ALT and ALP increased during the anaesthesia. As the values returned to the pre-administration level, the possibility of pathological changes in the liver could therefore, be ruled out. It corroborates with the findings of Koichev et al. (9) after detomidine administration in cattle and sheep. Changes in plasma electrolytes (Na⁺, K⁺, and Ca++) were only transient, and the values returned to near normal level after 24 h.

The combination of detomidine, midazolam, and ketamine produced satisfactory immobilisation and anaesthesia for umbilical surgery in calves, although some hypoxaemia and respiratory acidosis occurred. Muscle relaxation was good and no complications were encountered.

References