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Effects of preoperative carprofen on cardio-respiratory, hormonal and metabolic stress response in calves during umbilical surgery under isoflurane inhalation anaesthesia

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ABSTRACT

The aim of this study was to examine the effects of preoperative carprofen on the cardiorespiratory, hormonal and metabolic stress response during umbilical surgery under isoflurane anaesthesia combined with local anaesthesia, in calves. A randomised, blinded experimental study was conducted in 24 calves. Carprofen ($n = 12$; 1.4 mg/kg) or physiological saline solution (controls; $n = 12$) was administered 1 h prior to surgery. Anaesthesia was induced with xylazine (0.1 mg/kg, IM) and, after the onset of sedation (i.e. after 5–8 min), ketamine was administered (2 mg/kg, IV). Anaesthesia was then maintained with isoflurane (ISO) in oxygen to effect and completed by infiltration of the incision line with 20 mL of 2% procaine. Cardiorespiratory, endocrine and metabolic parameters were examined before, during and after surgery at short intervals.

In both groups, anaesthesia appeared adequate for the surgical intervention. Heart rate, stroke index and arterial blood pressure were significantly elevated after the onset of surgery. Oxygen partial pressure and oxygen delivery increased, while the oxygen extraction ratio decreased intraoperatively, ensuring sufficient oxygen supply. In the control group, the mean surge in serum cortisol concentrations tended to be higher ($P = 0.089$) and systemic vascular resistance (SVR) was significantly greater ($P < 0.05$) than in the carprofen group during surgery. In conclusion, the anaesthetic protocol used in this study induced reliable analgesia in both groups. The lower serum cortisol levels and SVR may indicate a reduced surgical stress response in calves undergoing umbilical surgery under ISO anaesthesia after administering carprofen preoperatively.

Introduction

Umbilical surgeries are among the most frequent abdominal interventions in calves and necessitate appropriate analgesic protocols (Virtala et al., 1996). Particularly for young animals, adequate perioperative analgesia must be ensured, since their insufficiently developed defense mechanisms against pain (inhibition, modulation) causes them to perceive pain more intensely (Pascoe, 2000). Furthermore, sensitisation mechanisms in newborns can be triggered by low-threshold stimuli (Benrath and Sandkühler, 2000). The best pain relief is achieved by combining different classes of analgesics (multimodal analgesia), which act upon different levels of nociceptive transmission (Muir and Woolf, 2001; Picavet et al., 2004; Anderson and Muir, 2005; Valverde and Gunkel, 2005; Coetzee, 2011). The additive and synergistic effects of such combinations provide effective pain relief, while simultaneously reducing the analgesic and anaesthetic dose needed, thus leading to reduced analgesic-related side effects (Picavet et al., 2004; Valverde and Gunkel, 2005). As isoflurane (ISO)-inhalation anaesthesia does not provide sufficient antinociception for surgical interventions (Pascoe, 2000), it must be used in combination with potent analgesics. In calves, α_2-adrenergic agonists such as xylazine, in combination with the dissociative anaesthetic ketamine, are commonly used (Rings and Muir, 1982; Picavet et al., 2004; Rioja et al., 2008; Abrahamsen, 2009). In addition, local anaesthesia is an effective method for intraoperative analgesia in cattle (Anderson and Muir, 2005) and is therefore a simple option for improving analgesia in ISO-inhalation anaesthesia. Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs) reduce sensory input from the periphery into the dorsal horn of the spinal cord due to the potent inhibition of cyclooxygenase (Hudson et al., 2008). In addition to this peripheral effect, NSAIDs such as carprofen also produce central analgesia via spinal and supraspinal mechanisms (Otto and Adams, 2005).

The aim of this study was to investigate the effect of carprofen, a NSAID, on the cardio-respiratory, hormonal and metabolic stress

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response to umbilical surgery in calves under xylazine–ketamine induction and isoflurane maintenance anaesthesia, along with local infiltration analgesia with procaine.

Material and methods

Experimental animals

Twenty-four Holstein–Friesian calves (six female, 18 male), aged 36.5 ± 8.9 days (mean ± standard deviation, SD) and weighing 56.4 ± 8.8 kg (mean ± SD) were used for the study. All umbilical hernias were corrected by an experienced surgeon (Baird, 2008). Hernia contents were reducible and diameters were <10 cm with a hernia ring of 1–3 cm and no signs of umbilical inflammation. Calves had no signs of other diseases on clinical examination. The uncomplicated nature of the hernias enabled surgeries to be performed in a planned time span of 60 min (60.20 ± 5.40 min; mean ± SD). The study was conducted in accordance with the guidelines of the Research Animal Act of the Lower Saxony Federal State Office for Consumer Protection and Food Safety (file number 33.9-42502-04-07/1343; approved September 14, 2007). All calves were acclimatised to the surroundings and handling 8 days prior to the surgery. They were housed in single pens with straw bedding and received water, hay and calf starter feed ad libitum, as well as whole milk (10% of body weight, BW) divided into four feeds per day. All calves were denied food but allowed water 12 h prior to induction of anaesthesia.

Study design and drug administration

In a blinded experimental study, calves were randomly allocated to carprofen ($n = 12$) or control groups ($n = 12$). Intravenous administration of 1.4 mg/kg carprofen (Rimadyl Rind, Pfizer Pharma) or an equivalent volume of sterile saline solution (0.9% NaCl) was carried out 1 h before induction of anaesthesia. All calves were premedicated with 0.1 mg/kg xylazine (Xylavet, cp-pharma) IM and after the onset of sufficient sedation (recumbency, ptosis), anaesthesia was induced with 2 mg/kg IV ketamine (Ursotamin, Serumwerk). In all calves, a rhomboid infiltration with 20 mL 2% procaine around the external umbilicus was performed. After endotracheal intubation (Tubus, blue line, ID 8.5, Smith Portex Critical Care), 2.5 vol% ISO in oxygen at a flow rate of 2 L/min was given, using a circle breathing system operated in a semi-closed mode. The calves were allowed to breathe spontaneously. After reaching a surgical plane of anaesthesia, the vaporiser setting was reduced to 1.5 vol% and ISO was provided to effect thereafter to maintain anaesthesia. The adequacy of surgical anaesthesia was assessed by the absence of palpebral reflexes, ventromedial rotation of the eyes, the absence of purposeful movements and reduction in skeletal muscle tone (Rugh et al., 1985). If there were purposeful movements or heart rate (HR), respiratory rate (RR) or mean arterial pressure (MAP) increased by >10%, ISO was increased by 0.5 vol%. If the parameters remained constant during a period of 15 min, ISO was reduced by 0.5 vol%. In general, the ISO supply was stopped when the last suture was completed, which was approximately 55 min after the surgery had started. Electrical heating pads and warmed NaCl-infusion (15 mL/kg/h) were used to maintain body temperature and to reduce the possibility of intraoperative hypothermia. The surgical stress response was documented by recording cardiorespiratory, endocrine and metabolic parameters. Cardiorespiratory parameters were measured in the operating theatre in the standing position (–90 min), in dorsal recumbency before the start of surgery (–30 min), and during surgery at 15 min intervals (0, 15, 30, 45, 60 min), immediately after surgery (0 min) and at 30 and 60 min postsurgery. For the last two measurements, the animals were unrestrained and free to resume sternal recumbency or standing position. Endocrine and metabolic parameters were also assessed in the stable 1 day prior to the operation (–24 h).

Rescue protocols for insufficient depth of anaesthesia, respiratory arrest and MAP <70 mmHg existed, but no such interventions were necessary.

Instrumentation

One day prior to the surgery, after surgical preparation and analgesia by local infiltration of local anaesthetic (2% procaine, Albrecht), an abdominal aortic catheter (45 cm long polyethylene tube, ID 0.86 mm, AD 1.52 mm, SIMS Portex; Meyer et al., 2010; Offinger et al., 2011) and an 8 F introducer set (Walter Veterinär-Instrumente) for the Swan–Ganz catheter were implanted into the left jugular vein (Offinger et al., 2012). For these procedures, no analgesics other than the local anaesthetic were used. All calves were administered 2.5 mg/kg enrofloxacin (Enro-Sleecol, Albrecht) IM for 3 consecutive days. On the day of the experiment, a 110 cm long, 7 F thermal dilution catheter with an in-line temperature sensor was inserted via the introducer and attached to a calibrated fluid-filled pressure transducer (Smith pvb, REF ST-37, Critical Care; Meyer et al., 2010; Offinger et al., 2012). At the thorax, the level of the scapulohumeral joint was marked in the standing animal and served subsequently as the zero level for the pressure transducer in the standing (Wagner et al., 1990; Amory et al., 1992; Lewis et al., 1999) and the recumbent animal. The thermodilution catheter was advanced until the tip of the catheter reached the wedge position in the pulmonary artery. Characteristic pressure waves (EKG-, AP-module M3001A; CVP-, PAP-, HZV-module M3012A, Philips Medizin Systeme) were used to confirm correct catheter positioning (Sprung, 1983). Permanent flushing with heparinised (10,000 I.E. Heparin/L, heparin-calcium-25,000-ratiopharm) saline ensured the patency of the measuring system.

Antinociception and use of isoflurane

A sufficient depth of anaesthesia was tested by deep pinpricks with an 18 G hypodermic needle before surgery. Purposeful movements during the surgery, if any, were recorded.

Expired end-tidal isoflurane (etISO) was sampled at the level of the y-piece (Gas module M1013A, Philips Medizinsysteme).

Endocrine and metabolic parameters

Serum samples for determining cortisol (Cortisol-immulite 1000-Test, Siemens Medical Solutions Diagnostic) and L(+)-lactate (Trinder-Method, Horiba ABX) were collected from the jugular vein and stored at –80 °C until analysis.

Cardiorespiratory parameters

Blood temperature, pulmonary wedge pressure, mean central venous pressure (MCVP) and mean pulmonary arterial pressure were measured via a thermal dilution catheter and MAP was measured via the aortic catheter. The cardiac output (CO) was determined by thermal dilution. A bolus of 5 mL ice-cold (0–5 °C) 5% glucose solution was injected at high speed via the proximal lumen of the catheter into the right atrium (Sprung, 1983). Five injections were carried out until three readings within a range of 10% were obtained and used to derive a mean value. The HR was determined via a lead II electrocardiogram. The RR was determined by counting the breaths per min, and the minute volume was measured with a volumeter.

Arterial blood (via the aortic catheter) and mixed venous blood (via the distal opening of the thermal dilution catheter) from the pulmonary artery were aspirated into heparinised tubes and stored on ice for blood gas analysis (Rapidlap 348, Bayer Diagnostic). Blood gas measurements were corrected for body temperature and hemoglobin concentration (Burnett and Noonan, 1974). The oxygen saturation of hemoglobin was derived from an algorithm developed for humans. Further variables were calculated as follows:

Cardiac index (CI; Skarda and Muir, 1996)

$$\text{mL/kg/min} = \text{CO/BW}$$

Stroke volume (Amory et al., 1992; Skarda and Muir, 1996)

$$\text{mL/beat} = (\text{CO/HR}) \times 1000$$

Stroke index (SI; Sprung, 1983)

$$\text{mL/kg/beat} = \text{stroke volume/BW}$$

Systemic vascular resistance (SVR; Amory et al., 1992; Skarda and Muir, 1996)

$$\text{dynes} \times \text{sec} \times \text{cm}^{-5} = ([\text{MAP} - \text{MCVP}]/\text{CO}) \times 79.9$$

Oxygen content (Sprung, 1983; Wilson et al., 1988)

$$\text{Arterial oxygen content (mL/dL)} = \text{Hemoglobin (Hb)} \times \text{arterial oxygen saturation} \times 1.36 + (p_aO_2 \times 0.003)$$

$$\text{Mixed venous oxygen content (mL/dL)} = \text{Hb} \times \text{mixed venous oxygen saturation} \times 1.36 + (pO_2 \times 0.003)$$

O_2 delivery (DO_2; Sprung, 1983; Skarda and Muir, 1996)

$$\text{mL } O_2/\text{min} = \text{CO} \times \text{arterial oxygen content} \times 10$$

O_2 consumption (VO_2; Sprung, 1983; Skarda and Muir, 1996)

$$\text{mL } O_2/\text{min} = \text{CO} \times (\text{arterial oxygen content} - \text{mixed venous oxygen content}) \times 10$$

O_2 extraction ratio (ER; Sprung, 1983)

$$\% = ([\text{arterial oxygen content} - \text{mixed venous oxygen content}]/\text{arterial oxygen content}) \times 100$$

Statistical analysis

Data were analysed using commercial software (SAS, version 9.3, SAS). Data are presented here as mean and standard error. To estimate the main effects and interactions of group and time, a two-way analysis of variance with one factor with repeated measures (ANOVA; SAS-Procedure GLM, Repeated-Statement) was used. Differences between each measurement and the baseline were tested using *t*-tests