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A BALANCED ANESTHESIA WITH A COMBINATION OF DEXMEDETOMIDINE, KETAMINE, BUTORPHANOL AND PROPOFOL FOR EXPERIMENTAL COMPRESSION ANASTOMOSIS IN SWINE

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ABSTRACT

Swine are increasingly used for experimental studies. This necessitates the development of effective anesthetic protocols adapted to this animal species and surgical intervention.

The aim of this study was to investigate the effectiveness of balanced anesthesia with Dexmedetomidine HCl, Ketamine HCl and Butorphanol tartrate premedication and propofol induction and Ketamine HCl and propofol maintenance.

Hematological parameters, respiratory and heart rates, SpO2 during compression anastomosis of the rectum were investigated.

The proposed method of balanced anesthesia provides adequate analgesia for performing compression anastomosis in swine.

Key words: swine, balanced anesthesia, compression anastomosis, propofol, ketamine.

Introduction

Swine are one of the most suitable experimental models for the development of many surgical techniques. This is because swine have many anatomical, physiological, and functional similarities with humans. Due to these qualities, swine are often used in experimental and scientific studies, as well as for the training of students in human and veterinary medicine, which leads to the development of new anesthetic protocols providing qualitative anesthesia and analgesia (Calzetta *et al.*, 2014).

Balanced anesthesia is the combined administration of different anesthetic agents with different mechanisms of action that interact with each other at different points along the pain pathway, resulting in additive or synergistic anesthesia and analgesia, with minor side effects compared to their individual administration (Elvir–Lazo *et al.*, 2010).

This study aimed to investigate the effectiveness of balanced anesthesia with premedication with Dexmedetomidine HCl, Ketamine HCl, Butorphanol tartrate and induction with propofol, and maintenance with Ketamine HCl and propofol.

Hematological parameters, respiratory and heart rates, and SpO2 during experimental rectal compression anastomosis in swine were investigated.

Materials and methods

The study was approved by the Committee on Animal Ethics of the National Veterinary Service in Bulgaria.

The study was conducted in the period 09.2021–01.2022.

Animals

Six healthy Bulgarian white swine (4 female, 2 male), weighing 42.3 ± 1.2 kg and 5.1 ± 0.9 months old, were obtained from an authorized and high–quality breeding farm in the district of Sofia and moved into the animal farm of the University of Forestry. Animals were randomly chosen from a homogeneous group to avoid significant individual variations concerning anatomy and physiology. Before the start of the studies, all animals were judged to be healthy on the basis of physical examination in order to include in the experiments only animals that were clinically healthy. All experimental animals underwent a two–week adaptation period in order to adapt to the environment and minimize the stress caused by the change of habitat. The animals were dewormed with Levamisole Hydrochloride (Levamisole® 7.5 %, Vetprom, Radomir, Bulgaria) at a dose of 0.0075 g/kg, s.c. During the study period, the animals were fed a winter ration corresponding to the norms for the animal category. They were fed a commercial pig diet (TopMix®, Kaloyanovo, Bulgaria) in combination with free access to hay.

Animals had no access to the water and feed 6 and 24 h before the surgery, respectively.

Anesthesia

Preanaesthetic agents

Preanaesthetic medications were an intramuscular combination of 0.02 mg/kg Dexmedetomidine HCl (Dexdomitor® 0,5 mg/ml; Orion Pharma, Espoo, Finland) and 10 mg/kg Ketamine HCl (Anaket® 10%; Richter Pharma AG, Wels, Austria) injected in one syringe. Ten minutes later it was injected intramuscularly 0.2 mg/kg of Butorphanol tartrate (Butomidor® 10mg/ml; Richter Pharma AG, Wels, Austria).

Induction and maintenance

A 25 mm 22 G was placed in the marginal auricular vein. After induction of anesthesia with intravenous 6 mg/kg propofol (Propofol–®Lipuro 1%; B. Braun's, Melsungen, Germany), the animal was intubated with an endotracheal tube. During the operative period, all animals breathed room air. All animals were submitted to fluid therapy with sodium chloride 0.9 %, 10 ml/kg/h (Natrii chloridum®, Actavis).

Anesthesia was maintained with propofol (0.04 mg/kg/h; Propofol–®Lipuro 1%; B. Braun's, Melsungen, Germany) and Ketamine HCl (4 mg/kg/h; Fentanyl Janssen; Janssen–Cilag Pharma, Wien, Austria) delivered by constant rate infusion.

Surgical procedure

After induction of full anesthesia, the pig is fixed in a supine position on the operating table. The operative field was prepared aseptically. The approach to the abdominal cavity was performed through a caudal median laparotomy. After gaining approach to the abdominal cavity, the rectum was palpated and part of it was brought outside the abdominal cavity. The intestinal segment to be resected was isolated by placing intestinal clamps. Enteroanastomosis was performed by placing a compression device between the two intestinal segments. After completion of the enteronastomosis, the abdominal wall was sutured routinely. The average duration of the operative intervention was between 60–70 minutes.

Measurements of the stress response

Heart and respiratory rate, SpO2

Heart and respiratory rate and SpO2 were monitored using the respective modules of a MEC–1000 VET patient monitor (Shenzhen Mindray Bio–Medical Electronics Co., Ltd). Measurements were recorded every 10 min on a multichannel chart recorder.

Hematological variables

Blood samples for hematological analysis were withdrawn anaerobically into K2 EDTA tubes before surgery and at 15, 30, 60, and 60 min after completion of surgery. They were analyzed immediately using a BC – 5000Vet analyzer (MINDRAY, China).

Statistical analysis

Statistical analysis was performed using the SPSS 23.0 Statistical Package (SPSS Inc# Chicago, IL, USA). Data are presented as mean+SD and a P value of <0.05 was considered significant. An independent t–test was used to examine hematological parameters, heart and respiratory rate, and SpO2 at different time points with the baseline (pre–surgical) levels.

Results

The sedation obtained by the administration of the preanesthetic agents allowed direct insertion of an IV catheter into the ear veins of all swine. All animals had a smooth induction of anesthesia. There were no deaths or complications during the course of the study.

Mean heart rate was 134±9.20 beats/min before surgery began. A gradual and significant decrease in mean heart rate was found throughout the entire period of surgery, with the lowest mean value found at the end of surgery (86.50±11.62) (Fig. 1).

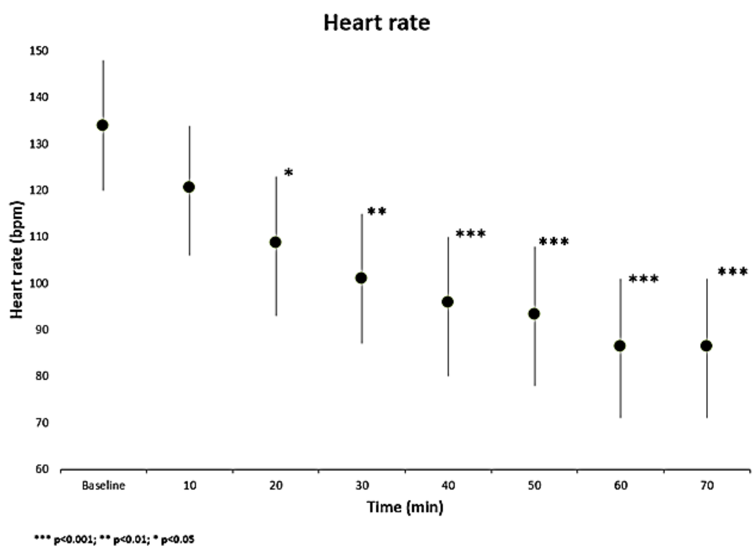

Figure 1: Mean heart rate during balanced anaesthesia with dexmedetomidine, ketamine, butorphanol and propofol in six swine. Values are means+SD, n=6.

The average respiratory frequency was significantly reduced from 20 min to the end of the operative intervention compared to the preoperative baseline frequency from 24.66±4.88 to 17.83±3.54 breaths/min (Fig. 2).

Mean SpO2 was 96.16±2.22 before the start of surgery, and a significant decrease was found between 40 and 50 min to 93.33±1.21 and 93.83±0.75, respectively (Fig. 3).

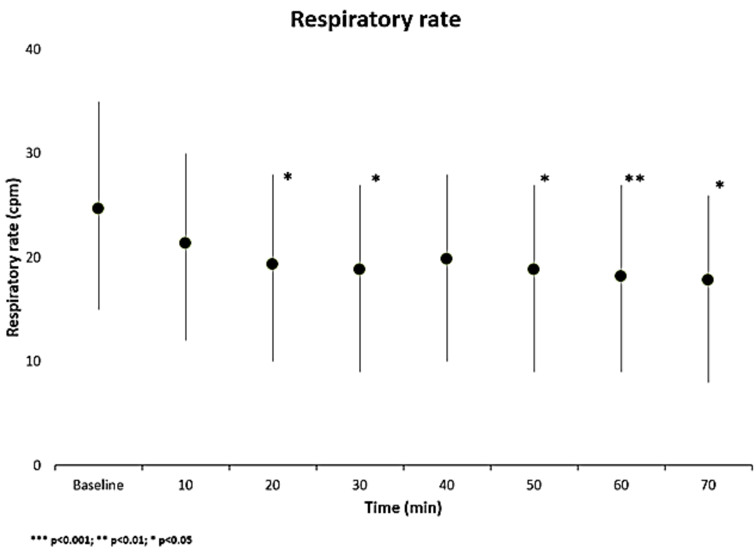

Figure 2: Mean respiratory rate during balanced anaesthesia with dexmedetomidine, ketamine, butorphanol and propofol in six swine. Values are means+SD, n=6.

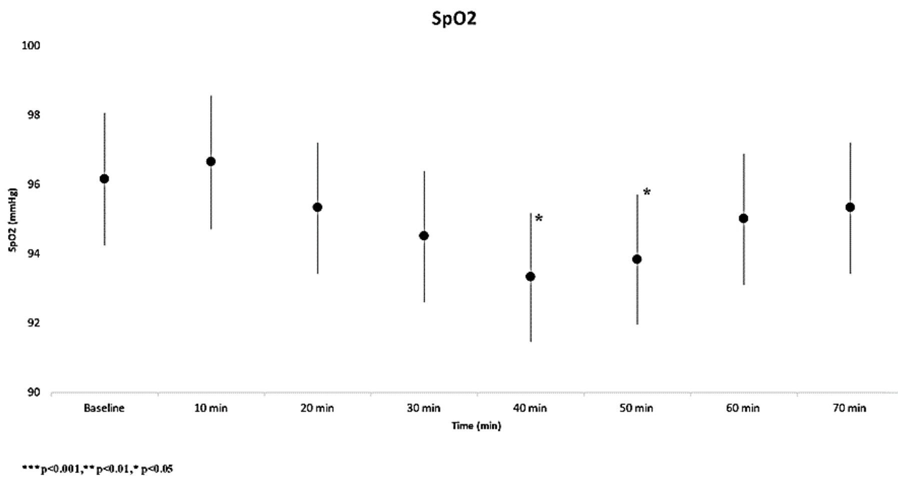

Figure 3: Mean Sp02 during balanced anaesthesia with dexmedetomidine, ketamine, butorphanol and propofol in six swine. Values are means+SD, n=6.

The surgery established a statistically significant reduction in RBC, HGB and HCT vs. baseline values. Only the values of HGB remained considerably lower by 60 min after the end of surgery (110.50±10.54). The lowest values were detected on the 15th min for RBC (6.28±0.28); HGB (105.6±3.14) and HCT (30.13±0.52) (Table 1).

Table 1: Changes in the values of RBC, WBC, PLT, HGB, HCT, MCV, MCH, MCHC during balanced anaesthesia with dexmedetomidine, ketamine, butorphanol and propofol in six swine. Values are means+SD, n=6.

Hematological variables

Parameters	Units	0 min	15 min	30 min	60 min	120 min
RBC	10^{12}/L	6.82±0.47	**6.28±0.28***	**6.20±0.27***	**6.20±0.40***	6.70±0.44
WBC	10^9/L	24.43±6.36	23.26±4.72	22.63±4.32	22.48±5.94	21.69±5.54
PLT	10^9/L	268.66±160.72	268.83±125.90	247.33±129.66	226.17±111.91	246.50±74.80
HGB	g/L	116±5.86	**105.6±3.14****	**106±8.46***	**106.83±6.46***	**110.50±10.54***
HCT	%	32.56±1.34	**30.13±0.52****	**30.2±2.08***	**30.17±1.99***	31.23±2.15
MCV	fL	48.50±2.63	48.11±2.08	48.16±1.97	48.13±2.24	47.78±2.73
MCH	pg	17.13±1.17	17.06±0.98	17.18±0.91	17.33±0.94	17.23±1.13
MCHC	g/L	352.66±12.72	353.33±8.64	351.50±12.34	356.33±9.73	356.16±8.13

*** p<0.001; ** p<0.01; * p<0.05

The mean white blood cell count was 24.43±6.36 and the mean PLT was 268.66±160.72 before surgery began. Neither variable changed significantly over time (Table 1), resulting in a mean WBC of 21.69±5.54 and a mean PLT of 246.50±74.80 60 min after the end of surgery.

Discussion

The present research demonstrated that the proposed novel balanced anesthesia protocol is effective, hemodynamically stable and safe in swine undergoing abdominal surgery.

Although some of the anesthetic agents used in this protocol, administered alone, usually cause cardiorespiratory depression (Bollen *et al.*, 2007; Duke, 1995; Hayashi et., 1994; Pypendop *et al.*, 1999; Smith *et al.*, 1997). The proposed balanced anesthetic protocol was very effective in maintaining hemodynamic homeostasis throughout the operation.

A number of studies in the field of analgesia have shown that the combination of different anesthetics and analgesics that have different mechanisms of action is highly recommended (Omamegbe and Ukweni, 2010; Ukwueze *et al.*, 2014; Pan *et al.*, 2021). The advantage of balanced anesthesia is the use of lower doses of the individual agents to obtain deep anesthesia and quality analgesia, thereby reducing the possibility of overdose.

The mean heart rate of the swine in this study decreased significantly (P<0.05) from baseline values (Fig. 1). Medetomidine hydrochloride is one of the drugs used in this study, causing hypertension that leads to physiologic sino–atrial and atrioventricular heart block and therefore bradycardia. Ketamine HCl is known to stimulate the cardiovascular system, like produces a sympathetic stimulation (Seliskar *et al.*, 2007), leading to tachycardia (Hall *et al.*, 2014). Hopster *et al.* (2014) found that the stimulatory effect of Ketamine HCl on cardiac activity was masked by coadministration with other anesthetics, such as α2–agonists. Therefore, Dexmedetomidine HCl may have suppressed the stimulant effect of Ketamine HCl, which is why that cardiac stimulant may not have stimulated the heart sufficiently to produce a heart rate that is up to the baseline value after the Dexmedetomidine HCl–induced bradycardia.

Propofol causes some respiratory and cardiovascular depression similar to thiopental. As such, it is not safer than it, but has the advantage that its effect is shorter and patients emerge from anesthesia more quickly (Hall *et al.*, 2014). Njoku (2015) found that intermittent propofol boluses caused a significantly lower heart rate compared to the continuous infusion technique, because at the time of bolus administration, the propofol plasma concentration is at its peak and its effect is maximal. The gradual ($P<0.05$) decrease in heart rate of the swine in this study from baseline may also be a result of the prolonged propofol infusion.

The respiratory rate decreased smoothly ($P<0.05$) from baseline from induction of anesthesia to recovery (Fig. 2). Jia *et al.* (2015) reported similar results. Respiratory depression has been reported as a characteristic complication of Dexmedetomidine HCl (Hall *et al.*, 2014), propofol (Wiese *et al.*, 2010), and Ketamine HCl (Hall *et al.*, 2014), all of which were used in this study.

Another study evaluated the anesthetic effect of a similar anesthetic protocol in swine, results similar to ours were obtained for the dynamics of SpO_2 (Fig. 3) during the anesthetic period (Lervik *et al.*, 2020).

Our study showed that the total number of erythrocytes and the content of hemoglobin and hematocrit in the selected balanced anesthesia protocol in swine were significantly reduced immediately after premedication and during the surgery (Table 1).

The decrease in the levels of these indicators is due to the action of anesthetic agents leading to suppression of the release of catecholamines and vasodilation of vascular smooth muscle (Wilson *et al.*, 2004). Zlateva *et al.* (2014) found that periods of falling cortisol and adrenaline levels were associated with lower HGB and HCT and reduced RBC counts.

Ketamine HCl and propofol have been found to induce smooth muscle vasodilation, altering vessel wall tone (Hall *et al.*, 2014). Changes in RBC, HCT, and HGB levels during anesthesia are due to vasodilatation of the splenic blood vessels that occurs due to the effects of the anesthetic agents used (Altura *et al.*, 1980).

Another reason for the change in red blood cell levels is the direct effect of propofol on red blood cells (Hall *et al.*, 2014).

Balanced anesthesia results in suppression of hemodynamic and immunological responses to surgical stimuli, and also provides effective pain control during and in the postoperative period by the administration of lower doses of the anesthetic agents used. Therefore, balanced anesthesia provides effective anesthesia and analgesia, reducing the probability of overdose of patients and providing suitable conditions for performing the operative intervention.

Conclusion

In conclusion, based on the obtained results, the proposed balanced anesthetic protocol allows for stable and safe anesthesia that is effective for experimental procedures in swine undergoing abdominal surgery.

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