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Changes of Vital Parameters after Administration of Butorphanol during Tiletamine-Zolazepam-Ketamine-Xylazine Anaesthesia for Joint Surgery in Miniature Pigs

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Abstract

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The study compares the effects of butorphanol in pigs undergoing joint surgery in tiletamine-zolazepam-ketamine-xylazine (TKX) anaesthesia. A total of 12 pigs were divided into 2 groups by 6 animals - BUT (anaesthetized with TKX combination and butorphanol) and CON (control group - anaesthetized with TKX combination only). All pigs were sedated with a mix of tiletamin-zolazepam-ketamin-xylazin, put into total anaesthesia using propofol, and connected to an anaesthesiology unit (O_2-Air). For 40 min we logged the heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), haemoglobin saturation by oxygen (SpO_2) and end-tidal CO_2 concentration ($ETCO_2$) values. Ten minutes after connecting to the devices, the pigs in the BUT group were intravenously administered butorphanol (0.2 mg/kg) in the total volume of 2 ml, or physiological saline in the same volume. The pigs in the BUT group had a lower ($p < 0.05$) HR in 5th, 10th and 25th min, and a lower RR in the 10th, 15th and 20th min. MAP, $ETCO_2$ and SpO_2 values did not differ substantially. Butorphanol can thus be identified as a suitable analgesic TKX supplement to anaesthesia of miniature pigs with minimum effect on vital functions.

Tiletamine-zolazepam, xylazine, ketamine, analgesia, cartilage lesion

Joint surgeries are very painful. High-quality balanced analgesia is thus the main prerequisite for correctly managed anaesthesia (Gaynor and Muir 2002).

Butorphanol is a mixed opioid agonist/antagonist (Pachter and Evens 1985) with quite a good analgesic effect (Pfeffer et al. 1980). It induces weak sedation, with a minimum negative impact on the cardiovascular system. It may cause a mild decrease of the heart frequency and arterial pressure, or respiration depression in animals (Greene et al. 1990; Trim 1983), which, however, is lower compared to morphine (Trim 1983; Hosgood 1990). Butorphanol effects become apparent within several min after intravenous administration. It remains in effect for approximately 2 - 4 h (Hosgood 1990).

The TKX combination (Henrikson et al. 1995) produces good anaesthesia in pigs, characterized by reliable and rapid induction and good cardiovascular function. These characteristics are very useful in laboratory environment, as easy handling to avoid stress is necessary for research. However, TKX did not provide superior analgesia. This is why we recommend potentiating analgesia with concurrent administration of suitable analgesics, e.g. butorphanol.

The effects of butorphanol administered in total anaesthesia combined xylazine-ketamine (Nishimura et al. 1992), tiletamine-zolazepam-xylazine (Ko et al. 1998), azaperone-ketamine and detomidine-ketamine (Brodbelt and Taylor 1999), xylazine-ketamine

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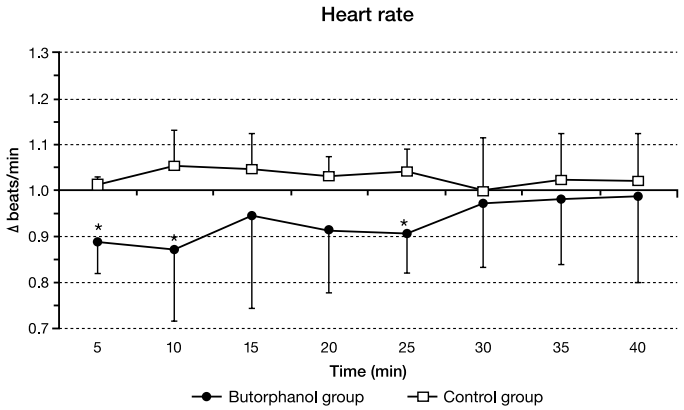

Fig. 1. Changes of the heart rate after butorphanol administration asterisk shows the differences ($p < 0.05$) between groups

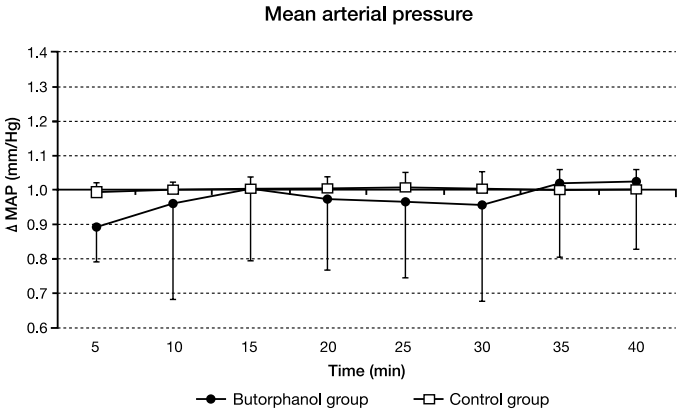

Fig. 2. Changes of the mean arterial pressure after butorphanol administration

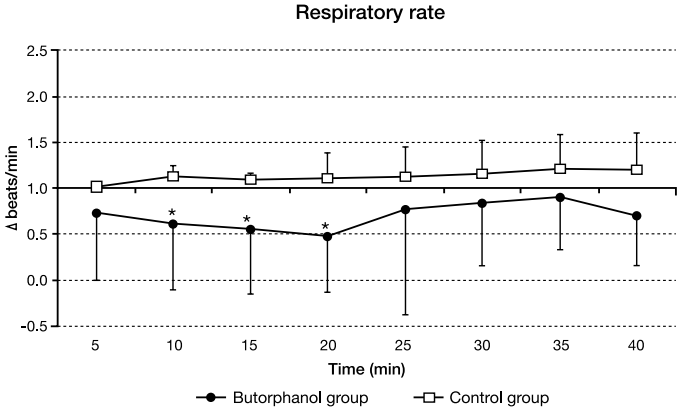

Fig. 3. Changes of the respiratory rate after butorphanol administration asterisk shows the differences ($p < 0.05$) between groups

(Nishimura et al. 1992) or medetomidine-ketamine were previously described in pigs (Sakaguchi et al. 1996).

The effects of butorphanol combined with a mix of TKX (tiletamine-zolazepam-ketamine-xylazine) in relation to vital functions in pigs have not been published yet.

Our objective was to detect and compare changes of heart and respiratory rates, mean arterial pressure, haemoglobin saturation by oxygen and end-tidal CO_2 concentration after butorphanol administration during TKX anaesthesia for joint surgery in miniature pigs.

Materials and Methods

Animals

All the anaesthetized animals served as control (in which osteochondral cartilage defects in stifle joints were created) in the experimental study of joint resurfacing using porous scaffolds seeded with mesenchymal stem cells (NPV II Research Project 2B06130). In the study, we used 12 miniature pigs - females aged 2.3 ± 0.62 years (mean ± SD), weighing 17.9 ± 3.64 kg. All pigs were clinically healthy. They were stabled in the location of experiment for 1 month before the experiment. During the whole study period, the animals were fed, handled and housed according to the principles of welfare. All procedures were carried out with the consent of the Ethics Committee (No. 46613/2003-1020).

Study design

This study was conceived as randomized non-blinded controlled study. A total of 12 miniature pigs were divided into 2 groups by 6 animals - BUT group (anaesthetized with TKX combination and butorphanol) and CON group (control group - anaesthetized with TKX combination only).

Protocol of experiment

Both groups of pigs were intramuscularly administered tiletamine-zolazepam (Zoletil 100, Virbac, France) at the dose of 2 mg/kg, xylazine (Sedazine, Fort Dodge, USA) at the dose of 2 mg/kg and ketamine (Ketaset, Fort Dodge, USA) at the dose of 2 mg/kg. All substances were administered together in a single syringe. After the start of sedation 10 min after administration, intravenous catheter with propofol was inserted in the ear vein (Propofol 1%, Fresenius, Austria) at the dose of 1 mg/kg, and an endotracheal tube was inserted in pigs. All pigs were put into the right lateral recumbency and connected to the inhalation circle rebreathing system. They were supplied with a mix of oxygen and air (1 : 1) in the amount of 25 ml/kg/min.

All pigs were connected to a vital functions monitor (Mindray PM-9000Vet, China). Monitoring equipment for this experiment was provided by BIOVENDOR Group, Czech Republic. The logged values included the heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), haemoglobin saturation by oxygen (SpO_2) and end-tidal CO_2 concentration ($ETCO_2$). HR was measured using a 3-lead ECG with electrodes located on the patient's chest. MAP was measured using a disposable blood pressure transducer (Mindray, China) connected to a monitor after calibration. The pressure transducer was connected to the arterial access port (a. auricularis on the contralateral ear to the venous access) using extension tubing filled with heparinized saline (200 IU heparin ml^{-1}, Heparin, Léčiva, Czech Republic). RR and $ETCO_2$ were logged using side-stream with a sensor connected to the tip of the endotracheal tube. SpO_2 was measured with a sensor connected to the patient's tongue.

10 min after connecting the animal to the anaesthetic machine, the BUT group pigs were administered butorphanol (Butomidor, Richter Pharm., Austria) at the dose of 0.2 mg/kg, diluted with saline to the total volume of 2 ml. The CON group was intravenously administered 2 ml saline at the same time.

All variables were measured right before the administration of butorphanol/saline (T_0) and every 5 min over 40 min (T_5 - T_{40}).

Statistical analysis

The homogeneity of the study groups was established by comparing baseline values (T_0) for HR, RR, MAP, SpO_2 and $ETCO_2$ using Kruskal-Wallis one way ANOVA. T_0 value was taken as value 1.0, values T_5 - T_{40} were logged as a proportional multiple of value T_0. The BUT group was compared with CON group by Wilcoxon-Mann-Whitney U-test. The statistical tests were two-sided and used a 0.05 type I error.

Results

When comparing the body weight and age of pigs, no significant difference was recorded between the BUT and CON groups.

HR values and their changes are shown in Fig. 1. In the BUT group, we recorded significantly higher HR values ($p < 0.05$) in the 5th, 10th and 25th min.

MAP values and their changes are shown in Fig. 2. Significant differences between BUT and CON groups were not recorded.

RR values and their changes are shown in Fig. 3. In the BUT group, we recorded significantly lower RR values ($p < 0.05$) in the 10th, 15th, and 20th min. In 2 animals of the BUT group apnoea occurred, requiring artificial ventilation.

$ETCO_2$ values oscillated depending on the RR. No significant differences in $ETCO_2$ values between BUT and CON groups were recorded.

Neither SpO_2 values did show significant deviations; no significant deviations between BUT and CON groups were recorded.

Discussion

In our study, we used butorphanol at the dose of 0.2 mg/kg intravenously, which is an average dose recommended by many authors (Brodbelt and Taylor 1999; Nishimura et al. 1992; Sakaguchi et al. 1992, 1996; Ugarte and O'Flaherty 2005). As reported by Greene et al. (1990) or Trim (1983), butorphanol effects on the cardiovascular apparatus are relatively small. In our study, we recorded a mild, yet significant HR decrease ($p < 0.05$) in pigs during concurrent administration of the TKX mix after butorphanol administration. Contrary to Greene et al. (1990) or Trim (1983), however, we did not encounter any blood pressure decrease. Lower HR values were recorded in the 5th, 10th and 25th min after butorphanol administration, which corresponds with the time of the onset of its effect reported by Hosgood (1990).

Ko et al. (1998) describe the butorphanol effect on anaesthesia in pigs, combined with tiletamine-zolazepam-xylazine, similarly to our study, but without ketamine. They do not mention HR deviation after butorphanol administration (which we recorded), but they mention a decrease of blood pressure that we did not encounter. Ko et al. (1998) also refer to breath depression requiring supplementation of pigs with oxygen, which corresponds to our study, although we used artificial ventilation.

Greene et al. (1990) or Trim (1983) also describe mild breath depression after the administration of butorphanol. In our case, however, breath depression was significant ($p < 0.05$) (in the 10th, 15th, and 20th min) and in 2 pigs it even required artificial ventilation. This does not fully correspond with the aforementioned facts; we can therefore assume that the breath depression was stronger due to the interaction of butorphanol and tiletamine-zolazepam-xylazine-ketamine effects.

Bibliographic citations about changes and mutual deviations of $ETCO_2$ are not available, our results cannot thus be compared. Brodbelt and Taylor (1999) mentions mild respiration acidosis with a SpO_2 decrease without substantial deviations between animal groups anaesthetized by the combination with butorphanol and without butorphanol. We did not record SpO_2 deviations between the groups of miniature pigs we monitored, either; however, we did not monitor the acid base condition of the organism.

When using similar anaesthetic combinations with butorphanol or without it in other animal species, the cited results are similar to our study, but not always entirely identical. Carroll et al. (1997) did not record in goats, similarly to O'Hair et al. (1988) in sheep, any differences between the groups of animals anaesthetized by the combination with butorphanol and without butorphanol. Greene et al. (1990) and Tyner et al. (1989) describe a significant HR and MAP decrease in dogs after butorphanol administration, which is identical to our results. Considering the aforementioned, we may assume that in relation to butorphanol, the pig behaves similarly to dogs, not like small ruminants.

From our results we may perceive butorphanol administration as a suitable supplement to total anaesthesia brought by TKX combination without a substantial effect on the haemodynamic functions of the patient. The respiration function is an exception which may be substantially suppressed.

The TKX combination with butorphanol is suitable namely for laboratory environment and handling to avoid stress, necessary for research projects. In addition, butorphanol

potentiates superior analgesia and anaesthesia, which is necessary in joint surgeries (Gaynor and Muir 2002), and it is insufficient when only the TKX combination is used (Henrikson et al. 1995).

Změny vitálních parametrů po aplikaci butorfanolu v průběhu TKX anestezie při operacích kloubů u miniaturních prasat

Studie je zaměřena na srovnání účinků butorfanolu u prasat podstupujících operaci kloubů v anestezii kombinací tiletaminem-zolazepamem-xylazinem-ketaminem (TKX). Celkem 12 prasat bylo rozděleno do 2 skupin po 6 jedincích - BUT (anestezovaná kombinací TKX a butorfanolem) a CON (kontrolní skupina - anestezovaná samostatnou kombinací TKX). Všechna prasata byla sedována směsí tiletamin-zolazepam-ketamin-xylazin, propofolem uvedena do celkové anestezie a napojena na inhalační anesteziologický přístroj (O_2-vzduch). V průběhu 40 min byly zaznamenávány hodnoty srdeční (HR) a dechové (RR) frekvence, středního arteriálního tlaku (MAP), saturace hemoglobinu kyslíkem (SpO_2) a koncentrace CO_2 na konci výdechu ($ETCO_2$). Za 10 min po napojení na přístroj byl prasatům skupiny BUT intravenózně podán butorfanol (0,2 mg/kg) o celkovém objemu 2 ml nebo fyziologický roztok o stejném objemu. Miniaturní prasata skupiny BUT měla v 5., 10. a 25. minutě nižší ($p < 0,05$) hodnoty srdeční frekvence a v 10., 15. a 20. minutě nižší hodnoty dechové frekvence. Hodnoty $ETCO_2$ a SpO_2 se výrazněji nelišily. Butorfanol lze proto označit za vhodný analgetický doplněk TKX anestezie miniaturních prasat s minimálním ovlivněním vitálních funkcí.

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