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Original article

Comparison of analgesia provided by lidocaine or morphine delivered epidurally in rabbits undergoing hindlimb orthopedic surgery

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Abstract

The aim of the study was to compare anaesthesia protocol utilizing combination ketamine/medetomidine with epidural lidocaine or morphine to orthopaedic surgery in rabbits. All rabbits received intramuscularly medetomidine (0.5 mg/kg) and ketamine (20 mg/kg). In group L (n=13) epidural injection was performed with lidocaine (3 mg/kg) and in group M (n=13) with morphine (0.1 mg/kg) diluted with sterile saline to 0.6 ml. Rabbits underwent bilateral mosaicplasty surgery. Heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP), arterial oxygen saturation (SpO_2) and respiratory rate (RR) were measured every 5 minute during surgical procedure. Duration of sensory blockade was measured based on toe pinch reflex and recorded.

Hemodynamic parameters were comparable at baseline in both groups. We did not observe significant differences in HR, RR, SBP, DBP, MAP between group L and M. Intragroup statistical analysis revealed differences at different time points in group M in terms of HR, SBP, DBP, MAP. In rabbits in group M blood pressure dropped while HR increased over time. In both groups a decrease in SpO2 was observed. Mean duration of loss of the toe pinch reflex was similar between group L and M, and amounted to 72.79±34.48 and 82.80±17.85 minutes, respectively.

Key words: epidural anesthesia, intraoperative pain, lidocaine, morphine

Introduction

Rabbits *(Oryctolagus cuniculus)* are very common anaesthetic patients. A wide range of breeds are kept as pets. They are also widely used for biomedical research due to their low cost of sustenance, easy venous access and a number of anatomical and physiological characteristics that are useful for research (Brodbelt et al. 2008).

Despite progress in the safety of small animal anaesthesia, rabbits are still considered difficult to maintain under general anaesthesia. A study into anaesthetic-

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-related deaths showed rabbits to be at an increased risk compared to dogs or cats (Morgan and Glowaski 2007).

Rabbits are highly susceptible to cardiac and respiratory problems under general anaesthesia. This rate of susceptibility may be due to the fact that doses of medications needed to induce and maintain anaesthesia are close to toxic doses. Moreover, rabbits reveal a variety of secondary effects related to stress and cardiac or respiratory reactions. Another factor leading to increased morbidity and mortality under general anaesthesia is difficult intubation due to the size and shape of the oral cavity, which prevents visualization of the larynx (Torske and Dyson 2000, Morgan and Glowaski 2007, Meylan et al. 2009). The greatest risks of ineffective, excessively forceful intubation are laryngospasm, laryngeal trauma, secondary swelling and vagal stimulation (Yaksh 1981).

Due to the high risk of general anaesthesia, local anaesthesia techniques are especially useful in rabbits. For hind limb surgery, epidural analgesia is recommended (Rawal and Sjostrand 1986, Valverde et al. 1991). Lidocaine has been widely applied as an epidural analgesic for intraoperative pain management, whereas morphine has been extensively used in postoperative pain management and to prolong analgesia induced by lidocaine.

The aim of the present study was to compare anaesthesia protocol utilizing combination ketamine/medetomidine with epidural lidocaine or morphine to orthopaedic surgery in rabbits.

Materials and Methods

The study protocol for the experimental use of the animals was approved by the Animal Care and Ethics Committee of the Wroclaw University of Environmental and Life Sciences (No. 95/2015). All rabbits underwent an experimental mosaicplasty surgery of both knees. After sterile preparation, a medial parapatellar arthrotomy was created. Using a mosaicplasty harvester, an osteochondral graft was harvested from the left and right medial femoral condyle. Subsequently, the grafts were transplanted to the contralateral knee.

After intramuscular premedication with medetomidine at 0.5 mg/kg (Cepetor, CP- Pharma Handelsges), general anaesthesia with intramuscular ketamine (20 mg/kg, Bioketan, Vetoquinol Biovet Pulawy) was induced. Rabbits were assigned to the L group (n = 13) or M group (n = 13) in a randomized blinded fashion. The rabbits of the L group received 2% lidocaine epidurally (Lignocainum Hydrochloricum 2% WZF, Polfa Warszawa) at a dose of 3 mg/kg, and the rabbits of the M group received morphine without preservatives (Morphini Sulfas WZF 0.1% Spinal, Polfa Warszawa) at a dose of 0.1 mg/kg diluted in sterile saline to 0.6 ml. Epidural anaesthesia was performed 15 minutes after ketamine administration. The epidural injection was performed into a intervertebral space between L7-S1 using a 50 mm, 20 gauge epidural needle. Correct placement of the needle was confirmed by the presence of a distinct 'popping sensation' as a result of penetrating the ligamentum flavum and the lack of resistance to injection. Anal sphincter relaxation was taken as confirmation of correct epidural drug administration. Before epidural drug application, aspiration was performed to avoid administration of the drug into vessels or intrathecal.

A twenty-three gauge catheter placed into the auricular artery was connected via saline-filled non-compliant tubing (regularly flushed) to a calibrated pressure transducer (zeroed level with the thoracic inlet) to obtain direct measurement of the heart rate, systolic, diastolic and mean arterial blood pressure (HR, SBP, DBP, MAP) (Datex-Ohmeda GE Healthcare S5). The margin auricular vein was cannulated, and saline (0.9% NaCl) was administered at a rate of 10 ml/kg/h throughout the procedure. Arterial oxygen saturation (SpO_2) was monitored using a pulse oximeter with a probe placed on the tongue (Datex-Ohmeda GE Healthcare S5). Rabbits were allowed to breathe room air spontaneously (FiO_2 0.21). The respiratory rate was measured by counting chest wall movements.

Intraoperative physiological variables were recorded every 5 minutes – first measurement was collected immediately after connection all monitoring devices (about 5-7 minute after epidural injection). Assessment of intraoperative nociception was based on changes in physiological variables above baseline value. Rescue analgesia consisted of IV fentanyl (2-3 mcg/kg, Polfa Warszawa S.A).

The criteria for fentanyl administration were based on an increase in heart rate, arterial blood pressure or respiratory rate >15% of the values before the beginning of the surgery, as well as sudden voluntary gross movements of the animals.

Intraoperative sensory blockade was assessed by clamping the tail, the base of the claw and the finger joint of both hind legs. Duration of sensory blockade was also assessed after the end of surgical procedure using the same methods. Assessment of sensation was performed every 5 minutes by the same, well-experienced anaesthesiologist. Time from epidural injection to returning sensation in the tail and hind limbs was recorded (RETURN TIME). In postoperative period all rabbits were carefully monitored for urine retention.

The results were expressed as the means ±SD. Repeated measures analysis of variance with Dunnet's

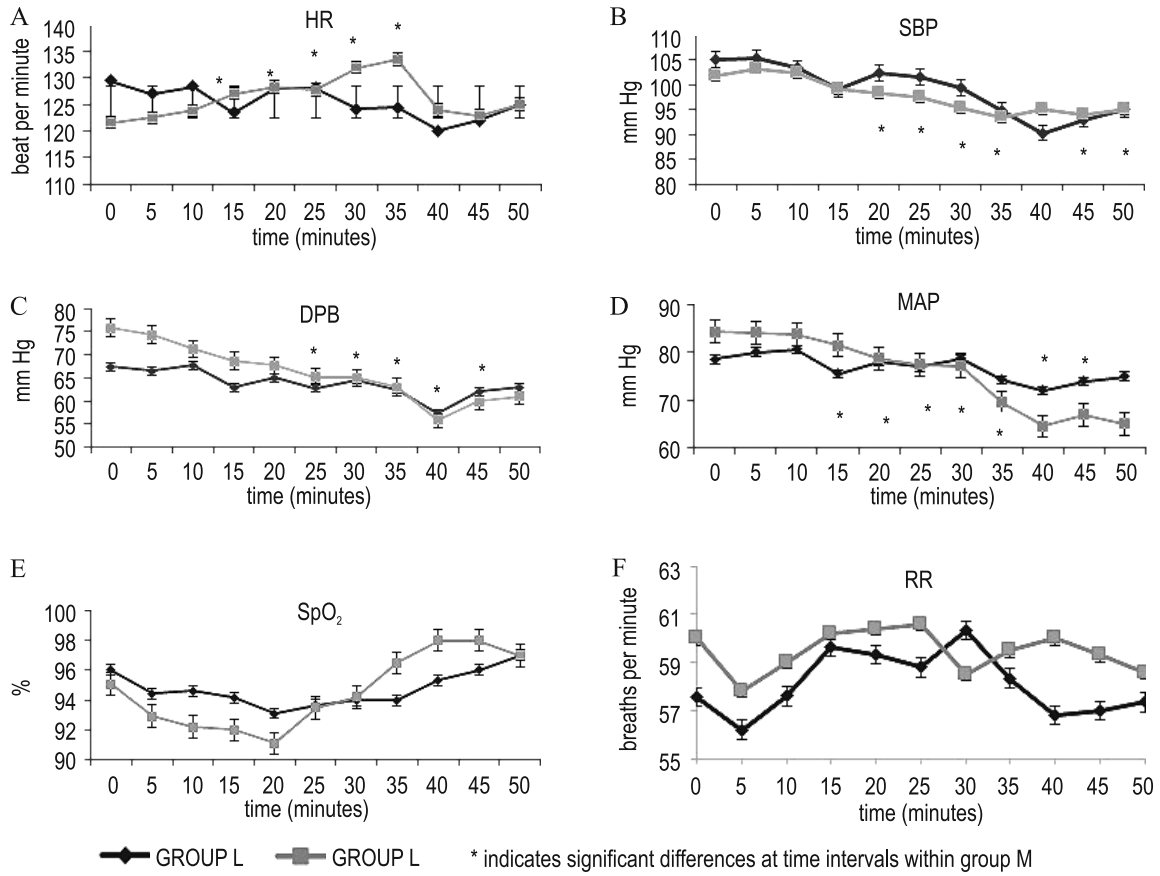

Fig. 1. Time course of heart rate (HR), systolic (SBP), diastolic (DBP) and mean (MAP) arterial blood pressure, saturation (SpO_2) and respiratory rate (RR) in group L (lidocaine, n=13) and group M of rabbits (morphine, n=13)

method for pairwise comparison was used for significant differences between time intervals when the data were not normally distributed. For normally distributed data, the repeated measures of analysis of variance with the Tukey test were used. In all cases, $p<0.05$ was considered significant.

Results

Epidural injections were successful each time. None of the rabbits required rescue analgesia. No urinary retention occurred in the postoperative period.

Return time was 72.79±34.48 and 82.80±17.85 minutes in group L and group M, respectively. There was no significant difference in return time between group L and group M ($p>0.05$).

Hemodynamic parameters were comparable at baseline in both groups (Fig. 1). At baseline, mean HR was 129.56 ± 21.05 bpm in group L as compared to 121.58±15.01 bpm in group M. Statistically, this difference was not significant ($p=0.26$). In group L, HR decreased from baseline to 120±11.35 bpm at 40 minute of surgery. This decreasing was not found to be statistically significant. In group M opposite trend was observed. HR slightly increased throughout the follow-up till 35 min when it reached 133.05±24.21 bpm, thus showing a mean rise of 11.47±7.87 bpm. This rise was statistically significant. However, intergroup comparison, at different time points, revealed that there was no significant change in HR during all procedure.

In terms of systolic blood pressure (SBP) there were no significant differences between the two groups at subsequent time points (Fig. 1B). In both groups SBP tended to be lower, although statistical significance was found only in group M. However, in group L the statistical significance was at the border ($p=0.05$). Intergroup differences also were not observed ($p>0.05$).

At baseline, diastolic blood pressure (DBP) was 67.39±12.39 mmHg in group L as compared to 75.38±12.39 mmHg in group M. Statistically, this difference was not significant ($p=0.06$). The decrease in DBP showed a declining trend to 40 min of procedure then slightly increase was observed in both groups. Statistically significant differences between the two groups were not observed, however, we found intragroup differences.

In group M, at baseline, mean DBP was 75.38±12.39 mmHg. A significant decrease in DBP was observed at

25 min interval itself (67.73±22.04) ($p<0.05$). The fall in DBP continued to increase throughout the follow-up till 40 min when it reached 56.00±17.89 mmHg, thus showing a mean fall of 19.38 mmHg ($p<0.05$). Within next 10 a slight increase was observed, however, DBP was still significantly lower than that at the baseline. Similar relationship was found in group L, however, the differences were not statistically significant.

In terms of MAP, there were no significant differences between the two groups (at baseline as well as at different time intervals) ($p>0.05$), but there were significant intragroup differences. In group M, at baseline mean MAP was 84.42±5.08 mmHg which decreased to reach 81.50±5.01 mmHg at 15 min, thus showing a decrease of 2.92±0.81 mmHg, though this change was statistically significant ($p>0.05$).

No significant differences between and intragroup were observed with respect to SpO_2. However, Fig. 1E show that there was a decreasing trend at 20 min in both groups. In subsequent time intervals SpO_2 increase was observed. In the last 10 minutes of procedure, SpO_2 exceeded baseline value in group L and in group M.

The respiratory rate within group L and M at different time points was found to be comparable. Statistical analysis also did not reveal significant differences between groups in terms of RR.

Discussion

Epidurally administered morphine has been extensively used for postoperative analgesia in both human and veterinary medicine. It has also been used as an adjunct to local anesthetics to prolong analgesic effect and has been demonstrated to provide a significant reduction in the amount of inhalant anesthetic needed to produce and maintain general anaesthesia in humans (Yaksh 1981) and in dogs (Valverde et al. 1991). However, there are limited reports of alone morphine usage for intraoperative pain. Rawal and Sjostrand (1986) concluded that spinally administered opioids are better for treating dull aching postoperative pain than acute intraoperative pain. Other scientists have paid attention to the other problems of morphine – there still has been no consensus on the optimal dose of intrathecal morphine when used alone (Torske and Dyson 2000, Meylan et al. 2009). However, spinally administered opioids have been reported to decrease inhalant anesthetic requirements in human patients during surgery (Yaksh 1981). This has been confirmed for epidural morphine in halothane-anesthetized dogs (Torske and Dyson 2000). We decided to compare the effectiveness of epidural morphine to intraoperative pain management with standard used lidocaine.

Assessment of intraoperative nociception was based on changes in heart rate, respiratory rate and arterial blood pressure 15% above baseline value. In group L changes in HR, RR and blood pressure were not significant. In none of the parameters considered a change above 15% was observed. No hypertension, tachycardia or tachypnoea were observed in group L. In group M, changes in RR were also not significant. HR increased by 10.84% between 0 and 35 min. However, as the changes in respiratory rate were not significant (below 15%) and blood pressure decreased, we assumed that an increase in heart rate was a compensatory mechanism for low blood pressure. Hypotension is a common side effect after epidural morphine and has been observed by many authors (Torske and Dyson 2000, Aminkov and Hubenov 2001, Moraca et al. 2003, Almeida et al. 2010, Stegmann 2010). The decrease in blood pressure is the result of a decrease in peripheral vascular resistance (Stegmann 2010). Except expected decreasing arterial blood pressure low SpO_2 was observed. Previous studies using ketamine and medetomidine combination have demonstrated that rabbits became hypoxic during anaesthesia (Hellebrekers and Sap 1997, Hedenqvist et al. 2002, Orr et al. 2005). In our study, pulse oximeter readings for oxygen saturation did not decrease below 91% – these findings are low but acceptable.

Assessing analgesic effect should also consider properties of the drugs used in premedication and induction, as both medetomidine and ketamine have analgesic properties. In rabbits, ketamine at a dose of 20 mg/kg given intramuscularly in combination with alpha 2 agonist, provides moderate surgical anesthesia for 30-40 minutes (Hedenqvist et al. 2002, Murphy et al. 2010). This moderate level of anesthesia and analgesia is suitable for diagnostic procedures or for short, less invasive surgical procedures, however, orthopedic surgeries require deeper anesthesia and stronger analgesia. In our research anesthesia obtained with ketamine enabled safe and painless epidural injection. Medetomidine-induced myorelaxation facilitated epidural injection as it reduced stiffness of the muscles caused by ketamine. Additionally, medetomidine also provided analgesia.

Duration of sensory blockade was 72.79±34.48 and 82.80±17.85 minutes in group L and group M, respectively. There were no significant differences between groups, however, obtained values were higher than those reported by other authors in study with lidocaine (Tavkoli and Kazemi-Mehrjerdi 2011, Marjani et al. 2014). In the present study, both in L and in M group, none of rabbits required rescue analgesia. Duration and level of analgesia was sufficient for bilateral mosaicplastic surgery. We did not observe intra- and postoperative complications. We conclude that both lidocaine

and morphine administered epidurally with ketamine/medetomidine combinations are useful and safe for orthopedic surgery in rabbits.

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