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EFFICACY OF EPIDURAL ADMINISTRATION OF MORPHINE WITH BUPIVACAINE FOR ORTHOPAEDIC SURGERY IN SHEEP

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The aim of the study was to test the hypothesis that epidural administration of morphine with bupivacaine provides more intense and sufficient perioperative analgesia compared with parenterally administrated butorphanol during orthopaedic surgery. Sheep were assigned to group C (control group, 6 sheep) and group E (epidural, 5 sheep). Sheep from group C were pre-medicated with midazolam (0.3 mg/kg, i.m.) and butorphanol (0.2 mg/kg, i.m.). Propofol was used for induction of general anesthesia in both groups. Sheep from group E were pre-medicated with midazolam, but without butorphanol. Sacrococcegeal epidural analgesia with morphine (0.1 mg/kg) and bupivacaine (1 mg/kg) was performed. We detected a significant increase in heart rate (19%, p=0.021) during surgery in group C. Two hours after surgery, the heart rate was 14.9% lower than prior to surgery in group E (p=0.017). In group E, throughout the surgery, we measured an insignificant increase in respiratory rate of 1.99%. In the same group, 120 minutes post surgery, we measured an increase in respiratory rate of 14.7%, while in group C there was a smaller increase of only 10.9%. The result from both groups was insignificant (p>0.05). The consumption of isoflurane in group C was higher than in group E by 27.3% (p=0.0043). The mean MAC was in group C higher by 27.6% as it was in group E (0.75% ± 0.25, 0.95 ± 0.3 in Group E and C, respectively). This distinction, according to the Mann-Whitney test, was not significant (p=0.329).

Key words: bupivacaine, butorphanol, epidural, morphine, sheep, stifle surgery

INTRODUCTION

Current attitudes about animal welfare have increased the importance of pain management in livestock. Even minor surgical procedures in livestock are now performed using a combination of regional, local, or general anesthesia combined with uninterrupted post-surgical analgesia (Ley *et al*., 1990). The majority of routine surgical procedures in ruminants can be done using local analgesics (Kumar and Chouhan, 1996). These techniques are simple, safe and

economical and do not require sophisticated equipment. Besides this, general anesthesia in this species often leads to tympanitis or regurgitation (Hashim and Hossain, 1989). Caudal epidural anesthesia also has many applications in sheep and goats, but the main practical use for an epidural in these animals would be correction of dystocia and reposition/retention of a vaginal and/or rectal prolapse. However, since caesarean section in these animals is usually performed in lateral recumbency, a higher epidural dose could also be used for this procedure, as well as for surgery on the hind limbs. The epidural technique used is much the same as in cattle, but it is sometimes harder to find the first intercoccygeal space, the most common place used is the sacrococcegeal space (S5-Co1) (Beltman *et al*., 2010). The most frequently used epidural anesthetic is lidocaine, but mepivacaine, bupivacaine, and procaine are also used. With the exception of bupivacaine, these agents provide analgesia of a relatively short duration and may necessitate re-administration of the agent to allow completion of the procedure (Day and Skarda, 1991). Epidural adminitration of agents with greater duration of action may be more appropriate for procedures requiring long acting analgesia. These agents include opioids and alpha-2 agonists (Luttinger *et al*., 1985; Eisenach *et al*., 1996). The half-time of elimination of butorphanol in the cow ranges between 1 and 2 hours (Dodman *et al*., 1992) and will provide 2-3 hours of postoperative analgesia and epidural morphine may provide 12-24 hours of postoperative analgesia (Riebold, 2002).

MATERIAL AND METHODS

Animals

After approval by the Ethical Committee for the handling of animals at the University of Veterinary Medicine and Pharmacy in Košice, 11 healthy adult female Merino sheep weighing from 33.5 kg to 52.0 kg were included in an orthopaedic research study involving surgical approach to the stifle joint and osteotomy of the proximal tibia. During the experimental period, all sheep were housed in a stall, fed with grass and hay and with free access to water. Sheep were assigned to group C (positive control group, six sheeps) or group E (epidural, five sheeps).

Study protocol

All sheep from group C were pre-medicated with midazolam (Midazolam® Torrex; 0.3 mg/kg, i.m.) and butorphanol (Butomidor® RICHTER PHARMA; 0.2 mg/kg, i.m.). Propofol (Propofol® 1% MCT/LCT Fresenius; 4 mg/kg, i.v.) was used for the induction of general anesthesia. The sheep from group E was pre-medicated with midazolam (Midazolam® Torrex; 0.3 mg/kg, i.m.), but without butorphanol. After induction of general anesthesia with propofol (Propofol® 1% MCT/LCT Fresenius; 4 mg/kg, i.v.), we applied epidural analgesia in this group. Each sheep was positioned in sternal recumbency and the skin over the sacrococcegeal area was aseptically prepared. The epidural analgesia was performed with a spinal needle (20 gauge) to the sacrococcegeal space (S5-Co1). We used a combination of morphine (Morphin® 1% Biotika) 0.1 mg/kg with bupivacaine (Marcaine® 0.5% spinal heavy) 1 mg/kg. There was a rescue dose of

butorphanol (0.1 mg/kg) prepared for the painful reactions during surgery. We used flunixin (Finadyne inj., SCHERING PLOUGH Sante Animale; 2.2 mg/kg) after observation in a post-operative period of 3 days. All animals were cannulated with a 20 gauge catheter and at a constant infusion rate of 0.9% saline solution (10 mL/kg/hour). For maintenance of general anesthesia during surgery, isoflurane (Isofluran® Torrex) in oxygen was used after endotracheal intubation. We used Komesaroff Mini-Kom anaesthetic machine with the vaporizer placed within the circuit. Heart rate (HR), respiratory rate (RR), and rectal body temperature (RT) were recorded before anesthesia, during the surgery at 10., 30. (osteotomy) and 60. minutes and 120 minutes after surgery. In Group E, duration of analgesia was assessed by the response to superficial muscular pinpricks over the whole hind legs. We evaluated muscle and tail relaxation on the basis of movement (flexion and extension of the hind legs and tail movement). We also measured onset of analgesia (min.), duration of analgesia (min.) and time needed to stand upright (min). During the surgery we recorded the following data: heart rate, respiratory rate, rectal temperature, and minimal alveolar concentration (MAC; %) of isoflurane. Data was recorded by a monitor (Mindray PM 9000 Vet). After surgery we measured the consumption of isoflurane by use of a graduated vessel and calculated it in mL/kg/60 min. The average length of surgery time was 74 minutes.

Statistical analysis

Heart rate, respiratory rate and rectal temperature were analyzed between groups by use of a 2-tail Student t test. Minimal alveolar concentration and consumption of isoflurane were analyzed by Mann-Whitney test. Significance was set at $p \leq 0.05$.

RESULTS

Physiologic variables

We detected a significant increase in heart rate (19%, $p=0.021$) during the osteotomy in the group without epidural. In the second group, there was an insignificant increase in heart rate of 11%. At 120 minutes after surgery, the heart rate was 14.9 % lower than prior to surgery in Group E. This change in frequency was significant ($p=0.017$). In Group C, 120 minutes post operative, an increase in heart rate was detected, but it was not significant. In Group E, throughout the surgery, we measured an increase in respiratory rate of 1,99 %. This increase was insignificant. In the same group, 120 minutes post surgery compared with pre-operative values, we measured an increase in respiratory rate of 14.7% while in Group C, there was an increase of only 10.9 %. The results from both groups were not significant ($p>0.05$). We observed tachypnoa in two sheep from group C during the tibial osteotomy and we gave a rescue dose of butorphanol (0.1 mg/kg, i.v.) and increased isoflurane MAC. At 120 minutes post surgery, Group E exhibited a 4.9% decrease in rectal temperature. The difference in group C was only 4.1%, meaning that the difference between the two groups was 0.8%. Although there was a statistically significant decrease in both groups, we do not

consider this as clinically relevant. Hypothermia (less than 37°C) was not detected in any of the sheep. Heart rate, respiratory rate and rectal temperature are sumarized in Table 1.

The volume of consumed isoflurane was being measured from the beginning to the end of the surgery in units mL/kg/60 min. The consumption of isoflurane in Group C was higher than in group E by 27.3%. This difference, according to the Mann-Whitney test, was very relevant (p=0.0043).

Table 1. Mean±SD heart rate (HR, beats/min.), respiratory rate (RR, breaths/min.) and rectal temperature (RT, °C) of the control group (C) and epidural group (E)

Variable		Time				
		pre-operative	intra-operative			post-operative
			10´	30 (osteotomy)	60´	
HR	C	78.7 ± 14.7	83.1 ± 9.5	93.6 ± 20.6	80.7 ± 12.9	88.2 ± 14.3
	E	81.8 ± 13.4	79.4 ± 14.8	72.8 ± 16.5	76.8 ± 11.3	69.6 ± 13.4
RR	C	27.3 ± 7.3	29.1 ± 6.9	30.5 ± 14.5	33.4 ± 9.2	30.3 ± 2.7
	E	31.2 ± 6.7	31.5 ± 8.4	31.8± 6.9	34.9 ± 11.1	35.8 ± 10.5
RT	C	38.9 ± 0.4	37.9 ± 0.9	37.2 ± 0.6	37.1 ± 0.5	37.3 ± 0.5
	E	39.1 ± 0.5	38.8 ± 0.6	37.8 ± 0.7	37.6 ± 0.7	37.2 ± 0.9

The mean MAC in Group C was higher by 27.6% compared to Group E. The MAC mean values for Group E and C were 0.75 % ± 0.25 and 0.95 ± 0.3, respectively. This distinction, according to the Mann-Whitney test, was not significant (p=0.329). The results of the volume of consumed isoflurane and minimal alveolar concentration of isoflurane in both groups are summarized in Table 2 and 3, respectively.

Table 2. The volume of consumed isoflurane in groups E and C during surgery

Group with epidural anaesthesia		Group without epidural anaesthesia	
sheep	the consumed isoflurane in mL/kg/60 min	sheep	the consumed isoflurane in mL/kg/60 min
E1	0.334	C1	0.527
E2	0.378	C2	0.428
E3	0.347	C3	0.455
E4	0.335	C4	0.426
E5	0.382	C5	0.398
-	-	C6	0.475
mean ± SD	0.355 ± 0.023	mean ± SD	0.452 ± 0.045
P value	0.0043		

Table 3. Minimal alveolar concentration of isoflurane in groups E and C during surgery

Group with epidural anaesthesia		Group without epidural anaesthesia	
sheep	MAC	sheep	MAC
E1	0.57	C1	1.28
E2	1.00	C2	0.61
E3	0.42	C3	0.83
E4	0.98	C4	0.87
E5	0.76	C5	0.76
-	-	C6	1.36
mean ± SD	0.746 ± 0.253	mean ± SD	0.952 ± 0.30
P value	0.329		

We administrated a combination of morphine and bupivacaine by epidural route after general anaesthesia in Group E. The onset of the effect was at an average of 13.2 minutes. In two sheep from this group, we did not observe any general attributes of epidural anaesthesia. The renewal of hind leg muscles reflexes was on average after 195 minutes. The sheep were able to stand after at an average of 372 minutes. All attributes of epidural analgesia in group E are summarized in Table 4.

Table 4. Effect of morphine and bupivacain on epidural analgesia in five sheep

Sheep	Onset of analgesia (min.)	Duration of analgesia (min.)	Ability to stand (min.)	Observations
E1	15	195	315	adequate muscle relaxation poor tail relaxation
E2	12	180	360	good muscle relaxation good tail relaxation
E3	10	195	405	good muscle relaxation good tail relaxation
E4	15	165	330	good muscle relaxation good tail relaxation
E5	14	240	450	adequate muscle relaxation poor tail relaxation
mean ± SD	13.2 ± 2.1	195 ± 28.1	372 ± 55.5	

DISCUSSION

We compared intra-operative and post-operative analgesic effects of epidurally administrated morphine with bupivacaine and systemic butorphanol for stifle surgery in sheep. The advantages of combining opioids and local anaesthetics include a higher percentage of reduction in inhalant requirements and longer and more complete analgesia that reduces postoperative use, but may also result in prolonged motor blockade associated with the use of local anaesthetics (Kona-Boun *et al*., 2006; Hendrix *et al*., 1996; Sibanda *et al*., 2006). Isoflurane MAC for maintenance of adequate depth of general anaesthesia was higher by 27.6% in the control group with the use of butorphanol. The requirement for the volume of isoflurane (mL/kg/60 min.) was decreased by 27.3% in the epidural group. Different agents appear to have a different duration of action. In an experimental comparison of bupivacaine and ropivacaine in dogs at a variety of concentrations, with or without epinephrine, a duration ranging from 103 min. (0.75 % ropivacaine) to 163 min. (0.75% bupivacaine) was observed by Feldman and Covino (1988). Based on needle pricking, we observed a minimal duration of 165 min for analgesia and maximal 240 minutes after surgery in Group E. Results of random trials comparing rates of cesarean delivery in women using epidural anaesthesia vs parenteral opioids by Sharma *et al*. (1997) and Muir *et al*. (1996) alleged that patient-controlled administration of intravenous opioids provides some comfort, however, patients receiving epidural analgesia were still more comfortable. If morphine is used in epidural injection, premedication with another opioid agonist is recommended (Egger and Love, 2009). Beneficial effects were documented by a study during which it was noted that goats given epidural morphine after stifle surgery vocalized less and were less likely to grind their teeth than goats that had no morphine (Pablo, 1993). In our study, sheep from Group E did not vocalize during recovery period, and all sheep in this group were duller and more depressed and the recovery period was prolonged. One sheep from the butorphanol group exhibited teeth grinding. After recovery more than 50 % of all sheep were bloated. Probably the reason was that every sheep recovered alone without a herd. Epidurally administrated analgesics provide longer and more effective analgesia with less side effects compared to systemic administration (Novello, 2010). We detected a significant increase in heart rate during the surgery compared to preoperative values in Group C. The heart rate was not significantly increased during the surgery after epidural analgesia. One study (Lucky *et al*., 2007) documented that sheep after epidural analgesia with 0.5% bupivacaine had not significantly decreased values of heart rate and respiration rate and after recovery the mean values of heart and respiration rate decreased significantly. Sherajee *et al*. (2003) detected significantly increased pulse rates after 5, 15 and 30 minutes of sedation and significantly decreased respiration rates at the same time in goats sedated with diazepam and administered epidural 0.5% bupivacaine alone. In our study, 120 minutes after surgery, the heart rate was 14.9% lower than prior to surgery in Group E ($p=0.017$). 3 sheep had tachycardia after surgery in Group C. We measured a not significant increase in respiratory rate throughout the surgery in Group E. After recovery, respiratory rates were lower in the control

group compared to the epidural group. Two sheep had hyperventilation after surgery in group E. Troncy *et al*. (2002) described respiratory depression, assessed by a decrease in rate which was higher in dogs receiving epidural injections of morphine alone as opposed to dogs receiving morphine and bupivacaine, although the former group was maintained at a higher inhalational anesthetic concentration, which could have contributed to this adverse effect. We did not observe any complications associated with epidural anaesthesia. The complications of general anaesthesia included regurgitation and tympany. All sheep ingested food after 24 hours without problems.

In conclusion, the combination of midazolam, epidural analgesia and inhalant anaesthesia provided better muscle relaxation and analgesia during orthopaedic surgery. Isoflurane MAC and consumption were less in the epidural group and these results are in agreement with earlier findings. Sheep are relatively stoical creatures and it is possible that they do not display obvious signs of pain and distress. Postoperative comfort appeared better for the epidural group, although the respiration rate was less in the butorphanol group.

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EFIKASNOST PRIMENE EPIDURALNE ANESTEZIJE KORIŠĆENJEM MORFINA SA BUPIVAKAINOM U ORTOPEDSKOJ HIRURGIJI OVACA

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SADRŽAJ

Cilj ovih istraživanja je bio da se testira hipoteza da epiduralna anestezija sa morfinom i bupivakainom omogućava intenzivniju i dovoljnu periopertivnu analgeziju u poređenju sa parenteralno primenjenim butorfanolom tokom ortopedskih hirurških zahvata. Ovce su bile podeljene u grupu C (kontrolna grupa, 6 ovaca) i grupu E (epiduralna, 5 ovaca). Ovce iz grupe C su prethodno primile premedikaciju midazolamom (0,3 mg/kg, i.m.) i butorfanolom (0,2 mg/kg, i.m.). Za opštu anesteziju je u obe grupe korišćen propofol. Ovce iz grupe E su primile premedikaciju midazolamom, ali bez butorfanola. Zatim je primenjena sakrokokcigealna epiduralna analgezija morfinom (0,1 mg/kg) i bupivakainom (1 mg/kg). U grupi C je tokom operacija registrovan značajan porast frekvence rada srca (19%, p = 0,021). Nakon 120 minuta od operacije, frekvenca rada srca je bila za 14,9 % niža nego pre operacije u grupi E (p = 0,017). Tokom operacija je u grupi E zapažen

beznačajan porast frekvence disanja od 1,99 %. U istoj grupi je 120 minuta posle operacije frekvenca disanja bila povećana za 14,7 %, dok je u grupi C, porast bio manji i iznosio je 10,9 %. Ova razlika nije bila statistički značajna ($p>0,05$). Unos izoflurana u grupi C je za 27,3 % bio veći nego u grupi E ($p = 0,0043$). Srednja vrednost minimalne alveolarne koncentracije izoflurana (MAC) je u grupi C bila viša za 27,6 % nego u grupi E (0,95% ± 0,3 i 0,75 % ± 0,25 respektivno). Ova razlika nije bila statistički značajna ($p = 0,329$, Mann-Whitney test).