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RESEARCH PAPER

A comparison of extradural and intravenous methadone on intraoperative isoflurane and postoperative analgesia requirements in dogs

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Abstract

Objective To compare the effects of intravenous (IV) and extradural (ED) methadone on end-tidal isoflurane concentration (F_E'ISO) and postoperative analgesic requirements in dogs undergoing femoro-tibial joint surgery.

Study Design Randomized, blinded, clinical study.

Animals Twenty-four healthy client-owned dogs undergoing surgical repair of ruptured cruciate ligaments.

Methods Dogs were randomly assigned to two groups of 12 animals and received either ED or IV methadone (0.3 mg kg^{-1} diluted with saline to 0.2 mL kg^{-1}). Pre-anaesthetic medication was IV acepromazine (0.05 mg kg^{-1}). Anaesthesia was induced with propofol and maintained initially with an F_E'ISO of 1.0% delivered in oxygen. Methadone was injected with the dogs in sternal recumbency; the observer was unaware of the administration route. At 10 minutes (stimulation 1) and 20 minutes (stimulation 2) after methadone administration pelvic limb reflexes were tested by digit-clamping. The time at skin incision (stimulation 3), joint-capsule incision (stimulation 4), tibial tuberosity drilling (stimulation 5), fabellar suturing (stimulation 6) and extracapsular tightening (stimulation 7) were noted. Changes in heart rate (HR) and respiratory rate and arterial blood pressure associated with surgery were recorded along with the corresponding F_E'ISO. After 20 minutes of anaesthesia, F_E'ISO was decreased to the minimum required to maintain stable anaesthesia. Immediately after tracheal extubation, 1, 2, 3 and 6 hours postoperatively and on the morning after surgery, the degree of pain present was assessed using a numerical rating scale. The HR, respiratory rates and blood pressure were also recorded at these times. Serum cortisol and blood glucose concentrations were measured before pre-anaesthetic medication and at each postoperative pain scoring interval except at 1 and 2 hours. Ketoprofen (2 mg kg^{-1}), carprofen (4 mg kg^{-1}) or meloxicam (0.2 mg kg^{-1}) were given by subcutaneous injection whenever pain scoring indicated moderate discomfort was present.

Results Controlled ventilation was required in six dogs which stopped breathing after IV methadone. The median F_E'ISO at stimulus 5 was 1.0% in the IV and 0.83% in the ED group. At stimulus 6, F_E'ISO was 1.0% in the IV and 0.8% in the ED group; the difference was statistically significant ($p \leq 0.05$). There was no significant difference in the duration of postoperative analgesia associated with administration route.

Conclusions Extradural methadone significantly reduces the isoflurane requirement compared with IV methadone during femoro-tibial joint surgery in dogs.

Clinical relevance Extradural methadone provides safe and effective pain relief in dogs undergoing cruciate ligament repair.

Keywords anaesthesia, analgesia, dogs, extradural, methadone.

Introduction

Pain alleviation in companion animals is commonly achieved using opioid analgesics. However, parenteral opioid administration is commonly said to cause undesirable side effects like sedation, bradycardia, respiratory depression, vomiting, defecation, urinary retention and ileus (Thurmon et al. 1996). The incidence of side effects is lower after extradural (ED) administration (Valverde et al. 1989) while ED opioid injection produces more profound and prolonged analgesia – and with smaller doses – compared with that provided by parenteral opioids (Skarda 1996; Thurmon et al. 1996). Extradural opioids obtund nociception without motor effects (Yeager et al. 1987). Thus, opioid drugs given by ED, rather than the intravenous route (IV), may (i) reduce the inspired concentration of inhalational anaesthetics required to maintain general anaesthesia; and (ii) lower the need for postoperative analgesia.

The effects of ED morphine are well documented in dogs, which, because of its high analgesic efficacy and long duration of action, is probably the most useful opioid drug for use by this route (Valverde et al. 1989). However, its onset of action is slow (Bromage et al. 1980). Like morphine, methadone is an opioid agonist with high OP3 receptor affinity. It is available as a racemic mixture of laevo-rotatory (L) and dextro-rotatory (D) forms in an aqueous, preservative-free solution with a pH of 6.64 (10 mg-ampullae; Heptadon, Ebewe Arzneimittel, A-Unterach, Austria). It is widely used in human beings for the management of cancer pain (Fainsinger et al. 1993; Ripamonti et al. 1997) and is given ED for postoperative pain relief and obstetrical manipulations (Beeby et al. 1984; Evron et al. 1985; Shir et al. 1990). Methadone has an onset-time of 10–20 minutes in human beings, which is faster than morphine, and it effectively controls pain for 7 hours (Bromage et al. 1980; Torda & Pybus 1982). In dogs, parenteral methadone (0.25–1.0 mg kg^{-1}) produces analgesia for 2–6 hours (Hall & Clarke 1991; Thurmon et al. 1996) and is commonly used in combination with tranquillizers, e.g. acepromazine, or sedatives, such as medetomidine or xylazine, to produce deep sedation (Nolan 2000). However, there appears to be little information on the ED use of methadone in dogs.

The purpose of this clinical study was to compare the effects of ED and IV methadone on intraoperative isoflurane requirements and the duration of postoperative analgesia in dogs undergoing anterior cruciate ligament repair.

Materials and methods

The study involved 24 client-owned dogs, nine males and 15 females, of various breeds, presented for surgery at the Veterinary University of Vienna with ruptured anterior cruciate ligaments. The owners gave consent for the investigation. Animals were judged to be healthy on the basis of physical and haematological examination. Medication with analgesic drugs at the time of presentation was recorded.

Animals were first examined in their kennels, with a view to obtain baseline HR and respiratory rates. The animal's temperament, pupillary diameter, and its reaction to haemostat application (to a pelvic limb digit) were also noted. A similar stimulus was used in all dogs and the haemostat was removed whenever pain reactions occurred. The ends of the clamp were taped to prevent injury. A catheter was placed in the cephalic vein and blood samples were taken for the estimation of serum cortisol and blood glucose. Pre-anaesthetic medication in all dogs was IV acepromazine 0.05 mg kg^{-1} (Vanastress; Vana GmbH, Vienna, Austria). After 20 minutes, anaesthesia was induced with propofol (Propofol 1% 'Fresenius'; Fresenius Kabi AG, Graz, Austria) injected slowly to effect (3–6 mg kg^{-1}). The trachea was intubated and anaesthesia maintained with isoflurane (Isofluran-Baxter; Baxter AG, Vienna, Austria) using a 60% oxygen-in-air mixture delivered using a partial rebreathing system. Heart rate [electrocardiogram (ECG)], respiratory rate (f_r), noninvasive arterial blood pressure (NIBP), end-tidal CO_2 tension ($P_E'CO_2$), O_2 saturation, oesophageal temperature and the end-tidal isoflurane concentration ($F_E'ISO$) were recorded every minute with an HP-CMS-monitor for anaesthesia (Hp Omni Care CMS Patient Monitor, Hp GmbH, Boeblingen, Germany). The dogs initially breathed spontaneously, but their lungs were ventilated whenever apnoea or panting occurred, and until

anaesthesia was stable. Animals were placed on a warming blanket (Care Quilt tm Blanket, Mallinckrodt Medical Inc., cd Juarez, Mexico) and throughout anaesthesia, a Ringer's lactate solution (Ringer-Lactat 'Fresenius'; Fresenius Kabi AG) was infused at 10 mL kg^{-1} $hour^{-1}$. Physiological variables were monitored for at least 3 minutes before methadone administration and every minute thereafter, for the duration of anaesthesia.

All dogs were prepared for ED analgesia: hair in the lumbosacral area was clipped and the dogs placed in sternal recumbency. Each was randomly assigned to receive methadone by either ED or IV injection, at a dose of 0.3 mg kg^{-1} using 10 mg mL^{-1} solution diluted with sterile saline to produce a total volume of 0.2 mL kg^{-1}. Extradural injection was performed at the lumbosacral (L7–S1) space. Correct spinal needle placement (22 SWG, 3 inches or 22 SWG, 2.5 inches) was confirmed by fluoroscopy, the absence of blood and, or CSF at the needle hub and a lack of resistance to injection. In both groups, methadone was injected over 2 minutes by an experienced anaesthetist who was not the observer. The observer was not aware of the drug administration route.

Nine minutes after methadone administration the dogs were placed in lateral recumbency and at 10 minutes (stimulation 1) and 20 minutes (stimulation 2) the nail bed of the pelvic limb was clamped for 1 minute to assess analgesia. The times at skin incision (stimulation 3) joint-capsule incision (stimulation 4), tibial tuberosity drilling (stimulation 5), fabellar ligament suturing (stimulation 6) and tightening the extracapsular stabilization (stimulation 7) were recorded. Alterations in f_r and HR and, mean arterial blood pressure (MAP) from 3 minutes before, until 5 minutes after each stimulus were recorded along with F_E'ISO values. For the first 20 minutes after methadone administration, F_E'ISO was maintained at 1.0%. After this, it was adjusted according to HR, f_r and MAP changes in response to surgery. End-tidal isoflurane levels were reduced every 3 minutes by decrements of 0.05%, based on the clinical assessment of anaesthetic 'depth' (eye reflexes, movement) and physiological variables. The goal was to achieve the minimum F_E'ISO compatible with a stable and adequate plane of surgical anaesthesia.

Intraoperative assessments and postoperative pain scoring was assessed in all dogs by a single observer. A numerical pain-scoring system was used which included behavioural indices, pupillary diameter changes and the ability to walk (Table 1). Pain scores were held to represent: 0, no pain; 1–6, mild pain; 7–12, moderate pain; 13–18, severe pain (see Popilskis et al. 1993). Objective physiological data, i.e. HR, f_r and MAP, were also recorded. Changes in these variables in response to clamping a digit of the normal pelvic limb, and the behavioural response to this were noted. Each stimulus was applied for 1 minute or until a pain response occurred, whichever was the earliest. Pain scores were also recorded at tracheal extubation (T0), 1 (T1), 2 (T2), 3 (T3), and 6 hours (T6) after surgery and on the first postoperative morning (T24). Heart and respiratory rates, MAP, proprioception, urination and defecation were also recorded at these times. Blood samples were taken for serum cortisol and glucose estimation at

Table 1 Numerical pain scoring system applied to dogs after surgery for repair of ruptured cruciate ligaments.

Observation	Score	Criteria
Appearance	0	No pain
	1	Mild pain
	2	Moderate pain
	3	Severe pain
Vocalization	0	Quiet
	1	Crying, responds to calming attempts
	2	Crying, no response
Movement	0	No movement
	1	1–4 position changes per minute
	2	Continuous position changes
Agitation	0	Asleep or calm
	1	Mild agitation
	2	Restless, uncomfortable
Response to stimuli	0	No response
	1	Slow response
	2	Turns head and pulls leg away
	3	Quick response, howling, rowling or snapping
Interactive behaviour	0	Too sedate to evaluate/normal
	1	Mildly sedated/appears anxious
	2	Slow reaction, depressed
	3	No reaction/aggressive
Ability to walk	0	Alone/too sedated to walk
	1	Walks with assistance
	2	Unable to walk
Mydriasis	0	No
	1	Yes

The maximum possible score (greatest pain) was 18. Scores of 1–6 were held to indicate mild pain, scores of 7–13, moderate pain; scores of more than 13, severe pain. Additional analgesics were given to dogs scoring 7 or more.

tracheal extubation, 3 and 6 hours after surgery and on the first postoperative morning for comparison with preoperative values. Cortisol levels were determined using competitive immunoassay (Immulite; DPC Biermann GmbH, Bad Nauheim, Germany) while blood glucose was measured by the Gluco-Quant test (Hitachi 911; Roche-Diagnostics, Vienna, Austria). Any dog with a pain score of, or greater than 7 at any time received either carprofen 4 mg kg^{-1} (Rimadyl; Pfizer Animal Health, New York, NY, USA), meloxicam 0.2 mg kg^{-1} (Metacam; Boehringer Ingelheim, Ingelheim, Germany), or ketoprofen 2 mg kg^{-1} (Romefen; Rhone Merieux, Lyon, France). Heart rates were obtained by electrocardiogram while blood pressure was measured by oscillometry; the tail cuff had a width-to-tail circumference ratio between 0.4 and 0.6. Both variables were monitored using a HP-CMS monitor. Respiratory rate was measured by observation of chest wall excursions. A final examination was performed when dogs were discharged some 24 hours later, and carprofen, meloxicam or ketoprofen given by subcutaneous injection depending on the animal's postoperative comfort levels. The same drug was then prescribed for oral use for a further 5 days.

Data were analysed using a Mann–Whitney *U*-test (M–W *U*-test) for nonparametric data with the probability of error of 5% ($p \leq 0.05$). Differences between animals for age and mass were tested using both a M–W *U*-test and a paired *t*-test. A chi-squared test for best fit was used to analyse the differences between group ED and IV concerning the number of dogs pre-treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and the duration of surgery.

Results

The mean (±SD; range) mass of animals studied was 27.3 ± 16.8; 8–79 kg. Their mean age was 7.54 ± 2.18; 2.5–10 years. There was no significant difference in age and masses of the dogs receiving pre-operative analgesics or in the duration of anaesthesia between the two groups. Mean time ± SD from administration of methadone to tracheal extubation was not different between groups (ED, 123.4 ± 38.3 minutes; IV, 125.2 ± 24 minutes).

Isoflurane requirements were significantly higher in the IV, compared with the ED group during stimulus 5 and 6 (Fig. 1). Dogs receiving pre-operative analgesics (five dogs in the IV group, eight dogs in the ED group) required more isoflurane when compared with other dogs. This was particularly evident in the ED group (Fig. 2). A time effect on end-tidal isoflurane requirement during surgery was demonstrated in operations lasting more than 121 minutes. Isoflurane requirement in the IV group was significantly higher during stimulations 5, 6, and 7 than in the ED group, whereas there was no difference between the two groups in operations lasting <121 minutes.

Heart rates were higher in the ED, than in the IV group at the beginning of surgery. Pre-operative analgesia did not influence HR during surgery in either group. During short duration procedures HR were significantly higher in the ED, than in the IV group. There was no intergroup differences during long operations. An increase in the median HR and median MAP during surgery was demonstrated in both groups. There were no statistically significant

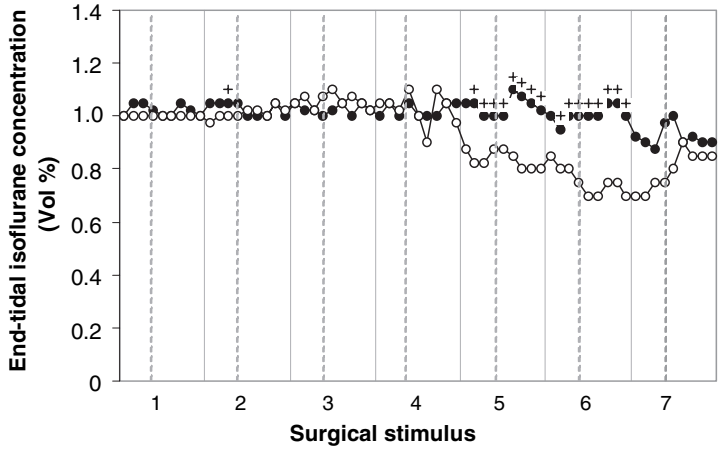

Figure 1 The median isoflurane requirements during anaesthesia recorded for 3 minutes before, during, and 5 minutes after each of the following stimuli: 1, toe clamping at 10 minutes; 2, toe clamping at 20 minutes; 3, skin incision; 4, joint-capsule incision; 5, tibial tuberosity drilling; 6, fabellar suturing; 7, tightening extracapsular stabilization. •, intravenous, ○, extradural; +, $p \leq 0.05$.

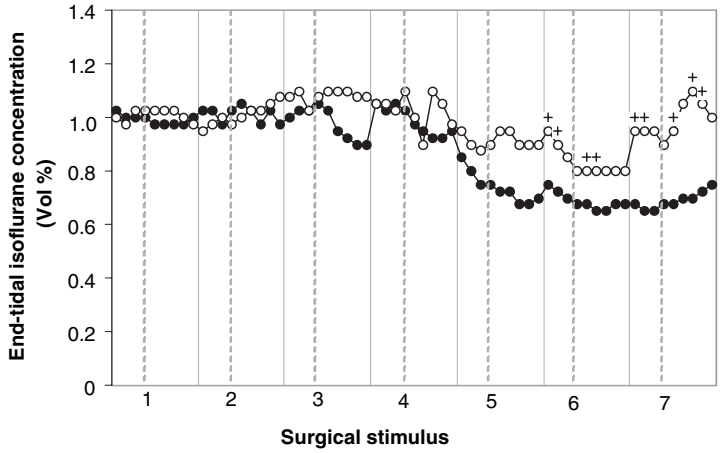

Figure 2 Comparison of the median isoflurane requirements of dogs with and without pre-treatment in the extradural group for 3 minutes before, during and 5 minutes after each of the following stimuli: 1, toe clamping at 10 minutes; 2, toe clamping at 20 minutes; 3, skin incision; 4, joint-capsule incision; 5, tibial tuberosity drilling; 6, fabellar suturing; 7, tightening extracapsular stabilization. •, without pre-treatment, ○, with pre-treatment; +, $p \leq 0.05$.

differences in median MAP values between the groups except for lower values at some time points in the ED group. Six dogs (IV) required intermittent positive pressure ventilation because they stopped breathing immediately after IV methadone injection.

There were no significant differences between the groups with respect to median subjective pain scores at any time point (Fig. 3). Heart rate changes at various stimulation points were greater in the IV group with statistical significance at T1 (1 hour after tracheal extubation) whereas differences in MAP were greater in the ED group 1 and 2 hours after tracheal extubation; these were not statistically significant. Panting occurred in several dogs making it impossible to compare postoperative f_r. Six dogs in the IV and nine in the ED group required additional analgesia within 6 hours of the end of surgery; times of administration are shown in Table 2. Although two dogs in the ED group received additional analgesics early in recovery, the mean time from methadone administration until additional analgesia was required (the duration of analgesia) was longer in the ED group (422.6 ± 108.3 minutes) than in the IV group (370.2 ± 93.2 minutes). This difference was not statistically significant.

Median cortisol values in the IV group were higher than in the ED group; differences were statistically significant at 3 and 6 hours. The largest increase from baseline values occurred at tracheal extubation in both groups and declined to reference values by 3 hours after tracheal extubation (Fig. 4). Median blood glucose values in the IV group were highest 3 hours after tracheal extubation in contrast to the highest values in the ED group, which were found at extubation (Fig. 5).

Undesirable side effects such as vomiting, pruritus or urinary dysfunction were not observed in any of the dogs. One dog urinated (IV) and one dog defecated (ED) intraoperatively.

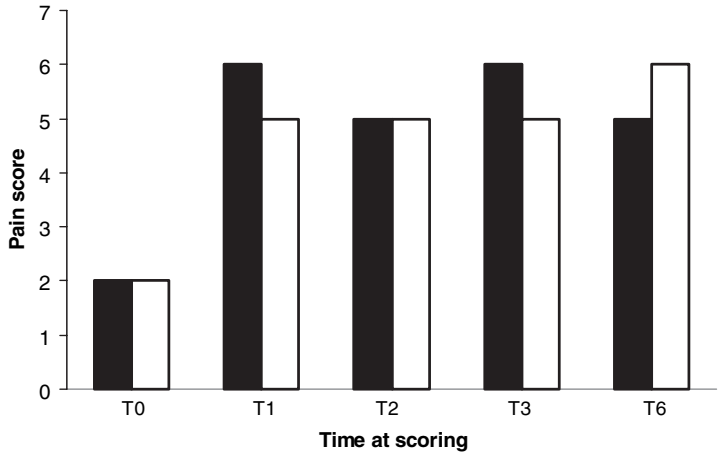

Figure 3 Median subjective pain scores in extradural (□) and intravenous (■) groups. T0, immediately after tracheal extubation; T1, 1 hour; T2, 2 hours; T3, 3 hours; T6, 6 hours after tracheal extubation.

Table 2 Timing of postoperative supplemental analgesia in dogs receiving extradural (ED) or intravenous (IV) methadone.

Time*	Dog number	Group	Time after methadone (minutes)	Pain score
T1	2	ED	241	9
T2	9	ED	222	10
T3	16	IV	321	7
	21	IV	302	7
	22	IV	298	7
	23	IV	325	8
T6	4	ED	562	7
	5	ED	449	7
	6	ED	442	7
	7	ED	458	7
	10	ED	475	7
	11	ED	508	7
	12	ED	466	7
	18	IV	463	7
	20	IV	513	8

*T1, 1 hour; T2, 2 hours; T3, 3 hours and T6, 6 hours after surgery.

Discussion

In human beings, ED methadone has fewer side effects and greater analgesic potency than ED morphine during Caesarean operation (Beeby et al. 1984). The shorter onset time of ED methadone probably reflects its higher lipid solubility, which allows faster uptake into the subarachnoid space (Bernards & Hill 1992). This property probably also accounts for its shorter duration of action in the ED space (Tung & Yaksh 1982). Its greater analgesic potency and low cost make methadone popular for parenteral use as an analgesic or in combination with tranquillizers to sedate animals.

Although the same operations (arthrotomy and extracapsular lateral stabilization of the femorotibial joint) were performed in each dog in the current study, different surgeons with different experience and expertise were involved. Consequently, the duration of surgery (from skin incision until tracheal extubation) varied and surgical stimulation occurred at different times. Therefore, the statistics we used differentiated between long (>121 minutes) and short (<121 minutes) operations, in addition to analyses without reference to time. In human beings, the onset time of effect of ED methadone, which is about 20 minutes (Cousins & Mather 1984) was taken to apply to dogs in the current study. Hence, the onset of analgesia was tested at 10 and 20 minutes after injection by clamping a pelvic limb digit while maintaining F_E'ISO at 1.0%. This concentration appeared to be suitable for maintaining stable anaesthesia for 20 minutes after methadone injection. There were no changes in either median HR or median MAP during this time. It is possible, however, that the clamping stimulus was innocuous, or that peak analgesia occurred before 10 minutes of injection, i.e. the F_E'ISO value of 1.0% could have been reduced earlier. The precise onset of extradural methadone activity could not be assessed from our data, but we nevertheless conclude that the analgesic effects of IV and ED methadone are comparable 10 minutes after injection. In some animals the 20-minute stimulus was replaced by skin incision (stimulus 3) but no differences in responses were observed. Noxious surgical stimuli such as skin or

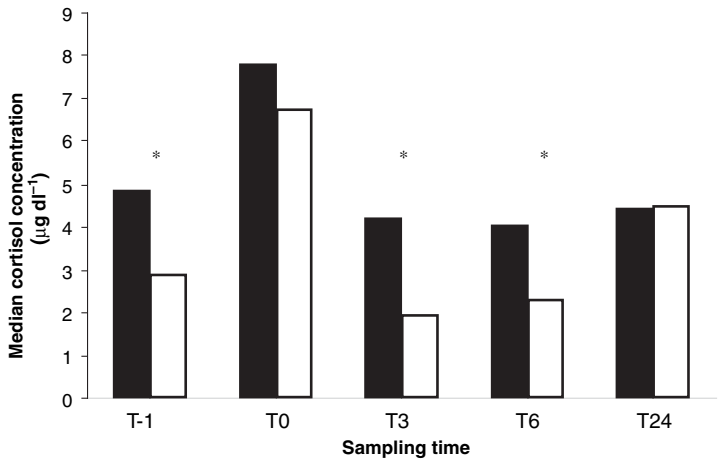

Figure 4 Median cortisol values in extradural (□) and intravenous (■) groups. T−1, before pre-anaesthetic medication, T0, immediately after tracheal extubation, T1, 1 hour; T2, 2 hours; T3, 3 hours; T6, 6 hours after tracheal extubation; T24, first post-surgical morning.

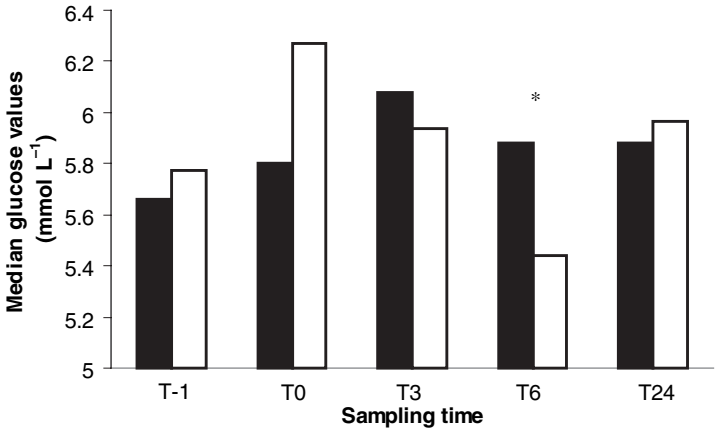

Figure 5 Median glucose values in extradural (□) and intravenous (■) groups. T−1, before pre-anaesthetic medication; T0, immediately after, T1, 1 hour, T2, 2 hours; T3, 3 hours; T6, 6 hours after tracheal extubation; T24, first post-surgical morning.

joint-capsule incision, tibial tuberosity drilling, fabellar ligament suturing or tightening of the extracapsular stabilization, appeared to be effective for evaluating isoflurane requirement.

All dogs were initially allowed to breathe spontaneously, in order that the respiratory effects of drug administration route could be determined. As a result, $P_E'CO_2$ levels varied and hypercapnia occurred in some dogs. Values of $P_E'CO_2$ up to 7.33 kPa (55 mmHg) were allowed providing f_r remained within physiological limits. Respiratory arrest occurred in some animals receiving IV methadone, necessitating positive pressure ventilation. Anaesthesia was probably too 'light' in one dog that panted; increasing the delivered isoflurane concentration restored a normal respiratory pattern. In contrast, ED methadone did not affect respiratory pattern. Opioid-induced respiratory depression is dose- and administration route-dependent but is usually of minor clinical significance (Jage 1990). In comparison with hydrophilic drugs, the rapid uptake of ED lipophilic compounds reduces their capacity to cause late respiratory depression (Shir et al. 1990).

Stable anaesthesia was maintained with lower $F_E'ISO$ values in animals receiving ED methadone compared with those in the IV group. The difference in isoflurane requirements between ED and IV groups was greater during tibial tuberosity drilling, and suturing of the fabellar ligament and may have been caused by higher intensity nocistimulation. Most dogs in the current study were suffering from cruciate ligament rupture of at least 1 week duration, but the finding that dogs which had received pre-surgical NSAID required higher $F_E'ISO$ values to maintain anaesthesia compared with those which had not, was unexpected. This effect was most obvious in the ED group. In combination with opioid drugs, NSAIDs reduce MAC value of isoflurane because of an additive or synergistic effect (Gomez de Segura et al. 1998; Ko et al. 2000). The exact role of NSAIDs on isoflurane requirements in dogs with ED or IV methadone is not clear, but an interaction is possible. In order to investigate this phenomenon a larger scale investigation is required.

Dogs in the IV group had significantly lower heart rates than those in the ED group during operations lasting <121 minutes, and there was a greater tendency to bradycardia. (However, HR remained within the physiological range in both groups.) Some dogs in both groups were moderately hypotensive during the first 20 minutes of surgery but MAP increased with surgical stimulation to values within the normal range. Thus, methadone (0.3 mg kg^{-1}) in combination with an isoflurane concentration of 1.0% caused hypotension, and surgical stimulation was required to increase MAP. It also increased HR in the IV group. Six dogs of the IV group required controlled ventilation, which meant that their values for f_r could not be compared with dogs receiving ED methadone.

The recognition and assessment of pain in animals is challenging, relying as it does on observing behaviour and measuring physiological variables. Different pain-scoring systems have been developed in order to make these observations objective. The pain-scoring system used in the current study was similar to other numerical rating systems that have been described for assessing pain in dogs (Conzemius et al. 1994; Sammarco et al. 1996; Walsh et al. 1999; Smith & Kwang-An Yu 2001). In order to avoid interobserver variability in

the subjective evaluation of behaviour, only one observer scored all dogs in the study. Dogs were examined by this observer before pre-anaesthetic medication and their behaviour assessed in preparation for further comparison. Behaviour and physiological variables, such as HR, f_r and MAP are affected by anxiety and fear, as well as pain (Conzemius et al. 1997), breed and individual characteristics (Holton et al. 1998). The need to urinate or defecate or the lack of human companionship can also cause vocalization and restlessness that may be misinterpreted as nociception (Hendrix et al. 1996). One dog in the current study was difficult to handle and its HR increased even when its neck was touched. A short interval was always required to allow the dog to get used to the observer, when it became sufficiently calm for accurate pain scoring.

In most dogs a slight mydriasis was observed during digit clamping, even when other behavioural or physiological responses were absent. Thus, the pupillary reaction may not have been caused by pain but may have been a reflex sympathetic nervous response to digit clamping. Postoperative lameness was probably caused by postoperative pain, although dressings may have exerted a mechanical effect. Although the same operative technique was used in all dogs, differences between surgeons may have increased the variability in postoperative pain scores. Two dogs in the ED group needed additional analgesia early in the postoperative period. The other dogs of this group that required supplemental analgesia, did so at 6 hours, which agrees with other studies examining the duration of action of ED methadone (Cousins & Mather 1984). Gourlay et al. (1982) suggested prolonged postoperative analgesia with IV methadone occurred because of its low clearance and long terminal half-life. This may explain why dogs in the IV group were less likely to require additional analgesia than those in the ED group, at least during the first six postoperative hours.

The assessment of objective postoperative variables was difficult. Respiratory rates were difficult to compare because several dogs panted at different time points in the evaluation. This may have been caused by higher ambient temperatures or excitement, and was not regarded to be indicative of pain. Technical difficulties prevented arterial blood pressure measurements being taken preoperatively, so there were no baseline values for comparison. Consequently, mean blood pressure and heart rate were only assessed postoperatively.

Serum cortisol and blood glucose were measured to assess their correlation with pain scores and to determine whether the route of administration had an effect. Cortisol concentrations in the current study were highest immediately after surgery; this has been described in previous studies (Popilskis et al. 1993; Hendrix et al. 1996). Popilskis et al. (1993) reported that animals receiving ED morphine had lower postoperative cortisol concentrations than those receiving IV morphine. Similar results were obtained in the current study: ED methadone appeared to be more effective in preventing postoperative stress or pain than IV methadone, at least on the basis of serum cortisol and blood glucose concentrations. The pain scores between dogs of the ED and IV group did not differ as markedly as cortisol and glucose values. It is possible that the scoring system was not sensitive enough, and that more variables should have been evaluated. No satisfactory explanation could be found for the significantly higher cortisol concentrations found in the IV group immediately before pre-anaesthetic medication, because dogs had not received any medication at this time.

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