

RESEARCH PAPER

Evaluation of analgesic and physiologic effects of epidural morphine administered at a thoracic or lumbar level in dogs undergoing thoracotomy

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Abstract

Objective To evaluate the analgesic and physiological effects of epidural morphine administered at the sixth and seventh lumbar or the fifth and sixth thoracic vertebrae in dogs undergoing thoracotomy.

Study design Prospective, randomized, blinded trial.

Animals Fourteen mixed-breed dogs, weighing 8.6 ± 1.4 kg.

Methods The animals received acepromazine (0.1 mg kg^{-1}) IM and anesthesia was induced with propofol (4 mg kg^{-1}) IV. The lumbosacral space was punctured and an epidural catheter was inserted up to the region between the sixth and seventh lumbar vertebrae (L, $n = 6$) or up to the fifth or sixth intercostal space (T, $n = 8$). The dogs were allowed to recover and after radiographic confirmation of correct catheter position, anesthesia was reinduced with propofol IV and maintained with 1.7% isoflurane. Following stabilization of monitored parameters, animals received morphine (0.1 mg kg^{-1}) diluted in 0.9% NaCl to a final volume of 0.25 mL kg^{-1} via the epidural catheter, and after 40 minutes, thoracotomy was initiated. Heart rate and rhythm, systolic, mean and diastolic arterial pressures, respiratory rate, arterial hemoglobin

oxygen saturation, partial pressure of expired CO_2 and body temperature were measured immediately before the epidural administration of morphine (0 minute) and every 10 minutes during the anesthetic period. The Melbourne pain scale and the visual analog scale were used to assess post-operative pain. The evaluation began 3 hours after the epidural administration of morphine and occurred each hour until rescue analgesia.

Results There were no important variations in the physiological parameters during the anesthetic period. The post-operative analgesic period differed between the groups, being longer in T (9.9 ± 1.6 hours) compared with L (5.8 ± 0.8 hours).

Conclusions The use of morphine, at a volume of 0.25 mL kg^{-1} , administered epidurally over the thoracic vertebrae provided longer lasting analgesia than when deposited over the lumbar vertebrae.

Clinical relevance The deposition of epidural morphine provided longer lasting analgesia when administered near to the innervation of the injured tissue without increasing side effects.

Keywords epidural analgesia, epidural catheter, opioids, pain management.

Introduction

Epidural administration of opioids is recommended in interventions that may cause intense and prolonged pain and lumbosacral morphine injections can provide analgesia for upper abdominal and thoracic procedures (Campoy 2004; Freitas et al. 2011). The epidural use of these drugs produces effective analgesia with localized and more intense effects when compared to systemic administration (Hansen 2001). The administration near to the site of action allows a reduced dose in comparison to systemic administration (Popilskis et al. 1993).

The duration of analgesia induced by epidural morphine in dogs and cats is about 8 to 24 hours, depending on the analgesic model and the pain assessment method used (Jones 2001). Lumbosacral epidural morphine administration was more effective than intravenous injection and produced pain relief for about 24 hours in dogs following thoracotomy (Popilskis et al. 1993). In dogs undergoing hemilaminectomy, topical administration of epidural morphine via an absorbable gelatin provided long term analgesic effects, lasting for at least 13 hours (Wehrenberg et al. 2009).

The benefits of thoracic epidural analgesia in humans are well described. The thoracic epidural route constitutes the most effective method to provide pain relief after abdominal and thoracic surgical procedures (Liu et al. 1998). Morphine administration through this route in thoracic surgeries reduced post-operative pain (Rudin et al. 2005; Tenenbein et al. 2008; Caputo et al. 2011) and the need for additional or systemic analgesic drugs during this period (Grant et al. 1993).

Thoracotomy is a surgical procedure associated with moderate to severe post-operative pain and marked impairment of respiratory function (Messina et al. 2009). Moderate degrees of hypoventilation and ventilation/perfusion mismatching in dogs have been reported (Stobie et al. 1995). Because pain is thought to greatly alter respiration after thoracic surgery, analgesics are essential in post-operative patient management. Opioids are still among the main drugs used in the control of pain due to their high effectiveness and safety (Hansen 2001; Smith & Kwang-An Yu 2001; Campoy 2004; Naganobu et al. 2004).

This study aimed to evaluate the analgesic effects and physiological parameters of epidural morphine administered at thoracic or lumbar levels in dogs submitted to thoracotomy. We hypothesized that

thoracic epidural morphine would provide better analgesia for thoracic surgical procedures.

Materials and methods

This study was approved by the Research Ethics and Animal Welfare Committee at the origin institution under protocol number 2009/85. Fourteen healthy, adult, male and female, mixed-breed dogs weighing 8.6 ± 1.4 kg (mean \pm SD) were used in the study. The health status was verified by clinical and laboratory (complete blood cell count and liver and kidney biochemical screening) examinations.

On the day before the procedure, the heart rate (HR) was measured in beats minute^{-1} (bpm), respiratory rate (f_R) in breaths minute^{-1} , systolic arterial pressure (SAP) in mmHg (Doppler vascular DV-10; Microem[®] Prod. Méd. Ltda, Brazil) and body rectal temperature (T °C; Termômetro digital; BD[®], Brazil). These data were considered as baseline parameters for post-operative evaluation (Melbourne pain scale), described later.

After a 12-hour fast, the animals were premedicated with 0.1 mg kg^{-1} of acepromazine (Acepran[®] 0.2%; UNIVET SA, Brazil) IM. After 20 minutes cephalic venipuncture was performed with a 22-gauge catheter and 4 mg kg^{-1} of propofol (Propofol[®]; Cristália Prod. Quím. Farm. Ltda, Brazil) was administered IV. The animals were positioned in sternal recumbency with the hind limbs extended rostrally. The lumbosacral region was clipped and surgically prepared. The lumbosacral space was punctured with an 18-gauge Touhy needle and a 20-gauge epidural catheter (Perifix - conjunto para anestesia epidural[®]; B. Braun, Brazil) was passed through it and advanced up to the sixth and seventh lumbar vertebrae (L, $n = 6$) or up to the fifth or sixth intercostal space (T, $n = 8$). The needle was removed and the catheter fixed to the skin using a patch (Cremer, Brazil). To confirm the correct position of the catheter, a lateral radiograph was taken after the administration of 0.5 mL iohexol (Omnipaque 300 mg mL^{-1} ; Farmasa, Brazil) via epidural catheter. After confirming the catheter position (mean period of 20 minutes), the animals were taken to the surgical center and anesthesia was induced with 4 mg kg^{-1} of propofol IV and an endotracheal tube was passed orotracheally and this was connected to a semiclosed circle system. The animals were positioned in lateral recumbency and anesthesia was maintained with 1.7% expired isoflurane (Isoforine[®]; Cristália Prod. Quím. Farm. Ltda, Brazil)

diluted in O₂ and mechanical ventilation with 15 cmH₂O pressure and inspiration/expiration ratio of 1:2 was used.

The physiological parameters were measured (PM 9000 Express[®]; Mindray Medical Brazil Limited, Brazil) immediately before the epidural administration of morphine (0 minute) and every 10 minutes during the anesthetic period. HR and heart rhythm, by lead II electrocardiography; mean arterial pressure (MAP), SAP and diastolic arterial pressure (DAP), through catheterization of a dorsal pedal artery with a 22-gauge catheter connected to a pressure transducer filled with heparinized saline solution and zeroed at the level of the manubrium; and arterial hemoglobin oxygen saturation (SpO₂), using a pulse oximeter on the animal's tongue. The f_R was adjusted so that the partial pressure of expired CO₂ (P_E'CO₂) was maintained between 35 and 45 mmHg (4.7–6 kPa - Poet IQ2 8500Q[®]; Criticare Systems Inc, WI). The T °C was kept between 36 and 38 °C with the aid of a thermal mattress.

After stabilizing the physiological parameters (15–20 minutes), the animals were positioned in dorsal recumbency and 0.1 mg kg⁻¹ of morphine (Dimorfi[®]; Cristália Prod. Quím. Farm. Ltda, Brazil) was administered via the epidural catheter (0 minute). This was diluted in 0.9% NaCl (Solução de cloreto de sódio 0.9%[®]; Hiplex Laboratório, Brazil), to a final volume of 0.25 mL kg⁻¹. After that, 0.5 mL of 0.9% NaCl was administered to prevent retention of the opioid solution inside the catheter. The animals were kept in the same position for 40 minutes to maintain the alignment of spinal cord and not influence the deposition of opioid and wait for the morphine latency period (Jones 2001). The animals were then positioned in right lateral recumbency to perform the thoracotomy at the fifth left intercostal space (parallel study).

Post-operative analgesia was evaluated by two trained observers, blinded to the treatments used, and began 3 hours after the epidural to avoid interference of residual effects from the drugs used in the anesthetic period. This was repeated at each hour until the administration of rescue analgesia. The Melbourne pain scale and the visual analog scale (VAS) were used to assess pain. The VAS used was a 100 mm line anchored at the left with 'no pain' and at the right with 'worst possible pain for this procedure' (Hansen 2003).

The Melbourne pain scale includes six categories: physiologic data (pupils, heart rate, respiratory rate, rectal temperature and salivation), response to

palpation, activity, mental status, posture and vocalization. The minimum score is 0 points, the maximum possible total pain score is 27 points (Firth & Haldane 1999). If the VAS average score was higher than 50 mm or Melbourne pain scale score was higher than 14 points, rescue analgesia with morphine (1 mg kg⁻¹ IM) and meloxicam (0.2 mg kg⁻¹ IM; (Maxicam 2%[®]; Ouro Fino Saúde Animal, Brazil) was administered. Animals that received rescue analgesia were removed from further data analysis but continued to be monitored to ensure adequate analgesia.

The statistical analysis used one-way variance analysis for paired samples with Dunnett's post test for comparison of mean values within each group in relation to 0 minutes. For comparisons between groups and time of rescue analgesia an unpaired *t* test was used. Physiologic values and time to rescue analgesia are presented as mean ± standard deviations. Pearson's correlation and Bland-Altman plots were applied to analyze observers variability on the VAS. Differences were considered significant for *p* < 0.05.

Results

The epidural catheter positioning technique was effective in all animals with no complications being observed during or after placement. Surgical procedures took 86 ± 12 minutes in T and 82 ± 11 minutes in L.

During the anesthetic period no important variations in the assessed physiological parameters were observed in relation to baseline or in comparison between groups at each time (Table 1). Post-operatively all animals, except one, received rescue analgesia because of high VAS scores. At the time of rescue, behavioral changes such as reluctance to move, attempting to protect the wound, restlessness, uncomfortable position, and indifference to eating were observed. With regard to the physiological parameters, only one dog showed heart rate, respiratory rate and blood pressures 50% above baseline values.

A statistical difference (*p* = 0.034) was observed between groups in the time to administration of rescue analgesia, being longer in the animals from group T (9.9 ± 1.6 hours) compared with group L (5.8 ± 0.8 hours) (Fig. 1). When rescue analgesia was administered (VAS higher than 50 mm), medians (interquartile range) of Melbourne scale score were 6.5 (2–11) for T and 6 (3–17) for L.

Table 1 Physiological parameters of dogs undergoing thoracotomy, maintained under isoflurane anesthesia and supplemented with 0.1 mg kg⁻¹ of epidural morphine at the thoracic (T) or lumbar level (L). Zero minutes corresponds to the time immediately before the epidural administration of morphine

Parameter	Group	Time (minutes)											
		0	40	50	60	70	80	90	100	110	120		
F _E /I _{SO} (%)	T	1.6 ± 0.2	1.7 ± 0.1	1.7 ± 0.2	1.7 ± 0.2	1.8 ± 0.1	1.8 ± 0.2	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	
	L	1.7 ± 0.1	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.3	1.8 ± 0.1	1.9 ± 0.2	1.8 ± 0.2	1.6 ± 0.5	1.9 ± 0.3	1.8 ± 0.1	1.8 ± 0.1	
HR (bpm)	T	96 ± 10	87 ± 17	95 ± 23	106 ± 18	107 ± 18	106 ± 17	108 ± 13	107 ± 11	107 ± 21	109 ± 18	109 ± 18	
	L	91 ± 10	92 ± 9	91 ± 17	102 ± 13	107 ± 22	109 ± 26	109 ± 28	116 ± 36	120 ± 43*	129 ± 58*	129 ± 58*	
SAP (mmHg)	T	91 ± 14	93 ± 22	104 ± 18	107 ± 11	101 ± 19	105 ± 17	103 ± 21	101 ± 12	101 ± 9	97 ± 6	97 ± 6	
	L	98 ± 11	92 ± 18	111 ± 8	105 ± 13	102 ± 13	98 ± 10	101 ± 8	96 ± 12	99 ± 8	97 ± 19	97 ± 19	
MAP (mmHg)	T	65 ± 6	67 ± 21	78 ± 17	82 ± 14	78 ± 16	77 ± 15	78 ± 20	74 ± 13	75 ± 11	73 ± 8	73 ± 8	
	L	66 ± 11	64 ± 16	83 ± 10	80 ± 15	74 ± 13	69 ± 8	68 ± 5	64 ± 7	67 ± 3	72 ± 3	72 ± 3	
DAP (mmHg)	T	50 ± 6	55 ± 21	65 ± 17	70 ± 16	66 ± 16	64 ± 15	64 ± 20	62 ± 15	61 ± 13	61 ± 9	61 ± 9	
	L	50 ± 12	50 ± 14	69 ± 12	67 ± 16	60 ± 13	54 ± 7	52 ± 5	50 ± 3	51 ± 5	60 ± 15	60 ± 15	
SpO ₂ (%)	T	97 ± 2	98 ± 1	96 ± 3	98 ± 2	96 ± 3	98 ± 2	98 ± 2	97 ± 4	97 ± 4	96 ± 3	96 ± 3	
	L	97 ± 3	96 ± 2	94 ± 4	95 ± 4	98 ± 1	96 ± 3	97 ± 3	98 ± 2	97 ± 3	99 ± 1	99 ± 1	

*Different from time 0 minutes ($p < 0.05$).

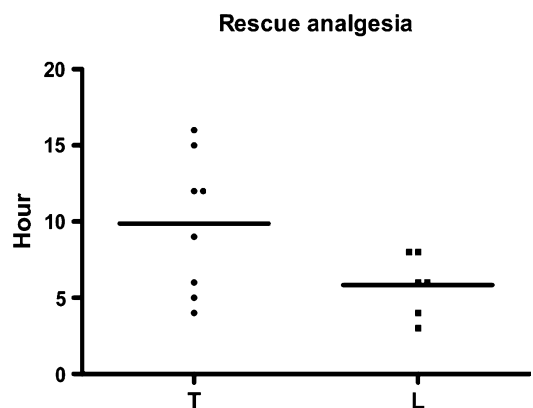


Figure 1 Time until rescue analgesia of dogs submitted to thoracotomy, maintained under isoflurane anesthesia and supplemented with 0.1 mg kg⁻¹ of epidural morphine at the thoracic (T) or lumbar level (L). The mean values are shown as the solid lines.

Pearson's correlation between observers with the VAS method was considered strongly positive ($r = 0.875$). A Bland-Altman plot showed a very good agreement between observers, limits being -16 and 11 (Fig. 2).

Only one of the animals from group L received rescue analgesia based on the increase in Melbourne scale and VAS parameters. This animal was markedly different from the others, needing additional analgesia after the administration of the described protocol, receiving a continuous infusion of ketamine (100 µg kg⁻¹ minute⁻¹ - Ketalar®; Parke-Davis, Brazil) and lidocaine (100 µg kg⁻¹ minute⁻¹; Xylestesin 2%®; Cristália, Brazil) for 3 hours subsequent to the initial rescue administration, although it demonstrated signs of improvement

after the first 15 minutes of infusion. No side effects or behavioral alterations were observed in any of the evaluated groups.

Discussion

Even though the placement of an epidural catheter is potentially harmful, due to direct trauma to the meninges or blood vessels during the insertion of the needle or catheter (Benzon 1993; Gibson 2004), no complications were observed during the epidural catheter insertion, nor after the catheter was positioned.

The cardiovascular parameters evaluated during the anesthetic period remained stable and within physiological ranges for both groups. Previous studies have shown that epidural administration of morphine blunts cardiopulmonary alterations in dogs anesthetized with halothane or isoflurane under controlled (Valverde et al. 1991; Keegan et al. 1995) or spontaneous ventilation (Troncy et al. 2002; Naganobu et al. 2004). However, these dogs were maintained at 1.5 × MAC of isoflurane which could blunt the cardiovascular responses to noxious stimulation, so this study does not clarify the degree to which the epidural opioid contributed to the lack of autonomic response in these animals.

Epidural opioids exert analgesic effects by diffusing through the meninges (McMurphy 1993). After epidural administration, the drugs undergo uptake by absorption into the cerebrospinal fluid and spinal cord, by sequestration into epidural fat or by systemic absorption through the epidural vascular network (Gourlay et al. 1987). Therefore, in addition to the effects in the spinal compartment (spinal

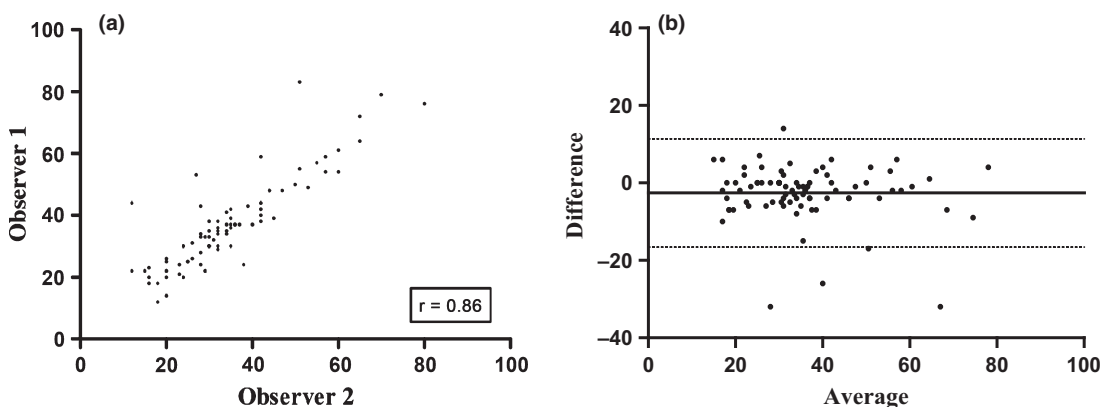


Figure 2 Pearson's correlation between observers (a), and Bland-Altman plot of difference between them (b), on post-operative VAS scores following thoracotomy. The dogs were maintained under isoflurane anesthesia and supplemented with 0.1 mg kg⁻¹ of epidural morphine at the thoracic (T) or lumbar level (L). The mean values are shown.

effect), systemic effects (supraspinal effect) are also expected (Valverde 2008).

Due to its low lipophilicity morphine administered epidurally has a long duration of effect providing both intra-operative and post-operative analgesia in this study, as well as in humans undergoing thoracotomy. Humans who received morphine by the thoracic epidural route needed a lower total dose than the lumbar epidural route in the first 24 hours post-operatively and this may be explained by the high morphine concentration that reaches the spinal segment where the nociceptive stimulus is greatest (Grant et al. 1993).

The longer time before post-operative rescue analgesia for animals in the thoracic group reflects the action of epidural analgesia at the site of administration and shows that analgesia results from a regional effect (Grant et al. 1993; Gold et al. 1997; Wehrenberg et al. 2009). Morphine administration by the lumbosacral epidural route provided analgesia for 24 hours in dogs undergoing thoracotomy (Popilskis et al. 1993) and for up to 16 hours in dogs submitted to different types of surgery (Troncy et al. 2002). Epidural administration at the site of injury provided analgesia for 13 hours in dogs submitted to hemilaminectomy (Wehrenberg et al. 2009) and in the present study analgesia was present for about 10 hours with the opioid being used near to the site of injury. It is believed that this difference in analgesia time is due to the different surgical stimulus in each situation and to the doses used, since the longest analgesic period observed was achieved using 0.15 mg kg^{-1} (Popilskis et al. 1993).

In this study we did the analgesic evaluation using the VAS and Melbourne scales because the two observers who participated in this study were trained and familiar with these scales, reducing the margin of error in the scores. The VAS proved to be more sensitive in assessing post-operative pain as most animals received rescue analgesia based on this method. Although the use of scales that require pain interpretation by an observer are difficult to apply in veterinary medicine, the VAS, even though subjective, is considered more sensitive than the simple descriptive scale and the numeric scale (Firth & Haldane 1999).

Because of the significant variability existing among observers for the use of three scales (simple descriptive scale, numerical rating scale and VAS) to assess pain in dogs, any analysis must incorporate observer variability when more than one observer is used (Holton et al. 1998a,b). Pearson's correlation

was considered strongly positive for the VAS and a Bland-Altman plot showed a very good agreement between observers. The correlation coefficient measures the strength of the relationship between the two sets of observations, but not the agreement between them. Bland-Altman recommends an alternative method for the analysis of such data, which is based on a simple graphic technique. Their approach involves plotting the difference between each pair of observations against the mean of that pair of observations. If the measurements made by each observer are exactly equivalent, the data points should lie along the line of zero difference, regardless of the mean measurement (Bland & Altman 1986; Christley & Reid 2003).

The Melbourne scale is based on unspecific behavioral and physiological response. But, the use of physiological parameters like heart rate and respiratory rate as well as pupil diameter did not prove to be useful pain indicators in hospitalized dogs (Holton et al. 1998a,b). In a similar way, the Melbourne scale used in this study was not satisfactory for recognizing pain in the animals, because it did not show high scores even when the animals had clear signs of pain and needed rescue analgesia based on the VAS.

In conclusion, the findings suggest that thoracic morphine deposition near to the innervation of the injured tissue provided a longer duration of analgesia in dogs undergoing thoracotomy, without side effects. The VAS scores were more useful in applying rescue analgesia than the Melbourne scale.

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