


STANDARD ARTICLE

Short-term efficacy of epidural pain management in dogs undergoing cystoscopy

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Abstract

Background: The effects of epidural anesthesia in dogs undergoing cystoscopy are unknown.

Objective: To investigate the effect of epidural analgesia on postcystoscopy pain in dogs.

Animals: Twenty-six dogs undergoing routine cystoscopy for lower urinary tract disease.

Methods: Prospective, randomized, blinded observational study. Dogs were assigned either to a treatment group that received epidural anesthesia (preservative free morphine sulfate, 0.09 mg/kg; 1% ropivacaine, 0.2 mg/kg; total volume delivered, 1 mL/4.5 kg of body weight to a maximum of 10 mL; n = 9) or to a nonepidural control group (n = 13). Vital signs were monitored for 24 hours, and sedation and pain scores, behavioral assessments, and presence or absence of complications was evaluated for 5 days postprocedure.

Results: All dogs tolerated the epidural without complications. Four dogs were removed from the study because of status unblinding, lack of patient cooperation, or incomplete follow-up. No significant differences were noted in postprocedural pain scores in dogs that received epidural analgesia. Significant differences in postprocedural pain scores were noted in the nonepidural control group. No significant differences were noted in vital signs, behavioral assessments, or the proportion of dogs with a 50% increase in pain scores between the epidural and nonepidural groups.

Conclusions and Clinical Importance: Epidural anesthesia was well-tolerated. Dogs not receiving the epidural had poor postprocedural pain control. A consistent benefit for the epidural vs nonepidural group could not be identified. Additional studies are required to better assess the impact and efficacy of epidural anesthesia for cystoscopic procedures.

KEYWORDS

canine, pain, urinary tract, urology

Abbreviations: MPS, Melbourne Pain Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; NRS, numerical rating scale.

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1 | INTRODUCTION

Rigid and flexible cystoscopy is used in small animal veterinary medicine for the evaluation of various types of urogenital diseases. Cystoscopy allows direct visualization of the urinary bladder and urogenital tract, allows minimally invasive tissue sampling, and in some instances accommodates minimally invasive treatments (eg, urolith removal, ectopic ureter correction). The indications, techniques, and benefits of this procedure are summarized elsewhere.¹

During a routine cystoscopic procedure, multiple passages through the urethra and into the bladder may be necessary and may result in a variable degree of iatrogenic trauma and occasionally clinically relevant cystitis, vaginitis, vestibulitis, or urethritis. These minor complications typically are self-limiting within the first week after the procedure, but during this time they may result in substantial postprocedural discomfort for the animal.^{1,2} An optimal pain management protocol for this procedure has not been developed or critically evaluated in veterinary medicine. Current recommendations for pain management include opiates, nonsteroidal anti-inflammatory drugs (NSAIDs), epidurals, antispasmodics, and topical anesthetics, and are based solely on expert opinion and experience.^{1,2} There are few evidence-based recommendations for pain management after cystoscopy despite the well-recognized discomfort reported in humans after this procedure.³

Our aim was to investigate the effect of lumbosacral epidural anesthesia in addition to standardized premedication and anesthetic protocols on postcystoscopy pain, discomfort, and need for sedation. A secondary aim was to monitor for complications and adverse effects related to epidural pain management. Our hypothesis was that the addition of a lumbosacral epidural to general anesthesia would improve postprocedural comfort in study animals with minimal adverse effects.

2 | MATERIALS AND METHODS

Eligible dogs were enrolled in a prospective, randomized, blinded observational study performed at The Ohio State University Veterinary Medical Center. The study design was approved by the Institutional Animal Care and Use Committee at The Ohio State University. Client-owned dogs >4 months of age undergoing routine cystoscopy as part of a diagnostic evaluation were eligible to participate in the study. Informed consent was required by owners for study participation.

All enrolled dogs were deemed systemically healthy based on physical examination, historical data, and available diagnostic results after assessment by a board-certified internist (J. Byron, A. J. Rudinsky). In each individual dog, diagnostic testing was performed at the discretion of the attending clinician. All dogs were required to have a CBC, serum biochemical panel, urinalysis and urine culture, and abdominal ultrasound examination. In selected cases, computed tomography with excretory urogram, urogenital biopsy with histopathology, and other diagnostic tests were performed at the discretion of the attending clinician. Dogs were excluded from the study if evidence of clinically relevant nonurinary disease was apparent on any diagnostic test performed. Additional exclusion criteria included inability to receive

NSAIDs for postprocedural pain management, behavioral problems that precluded enrollment, and clinically relevant orthopedic disease or neurologic deficits that could interfere with normal ambulation and pain perception or expression.

Dogs were randomly assigned to a treatment group that received a lumbosacral epidural preprocedure (preservative free morphine sulfate [Cardinal Health, Dublin, Ohio], 0.09 mg/kg; 1% ropivacaine [Cardinal Health], 0.2 mg/kg; total volume delivered, 1 mL/4.5 kg of body weight to a maximum of 10 mL) or a control group that did not receive an epidural but otherwise underwent the same anesthetic regimen, procedural preparations and sham needle puncture. After a preanesthetic physical examination, body weight, rectal temperature, pulse, respiratory rate, mucous membrane color, hydration status, and an American Society of Anesthesiologists preoperative status were determined.⁴ Regardless of group, dogs were given acepromazine (0.02-0.1 mg/kg IM; MWI Animal Health, Boise, Idaho) and morphine (0.4 mg/kg IM; Cardinal Health) as anesthetic premedications. Anesthesia was induced with propofol (3-5 mg/kg IV; Cardinal Health) given to effect through a peripheral catheter before intubation. Anesthesia was maintained using inhalant isoflurane (Akorn, Lake Forest, Illinois) and vascular support by IV crystalloid fluid administration. Patient monitoring was performed and data recorded every 5 minutes from induction until recovery. Carprofen (Rimadyl, Zoetis, Kansas City, Missouri) was administered at a dosage of 2.2 mg/kg PO or SC q12h starting with a SC injection during anesthetic recovery and then PO starting the morning after the procedure for a total of 4 doses. Epidurals were performed and anesthetic protocols designed by 1 of 2 board-certified anesthesiologists (T. Aarnes, P. Lerche). Briefly, after skin preparation, the epidural was performed with the patient in sternal recumbency with the hindlimbs positioned cranially. The lumbosacral space was identified based on anatomic landmarks (craniodorsal aspects of the wings of the ilium and location of the last palpable space between vertebrae). The epidural space was confirmed with either a hanging drop, loss of resistance to injection, or both. The hanging drop technique is assessed by aspiration of fluid from the hub of the needle as it enters the epidural space.

Investigators and owners were blinded as to whether each dog had received an epidural. Dogs in both groups had hair in the lumbosacral region clipped, and dogs in the control group received a sham needle puncture to maintain blinding throughout the observational period. Cystoscopy procedures were begun between the hours of 10:15 am and 2:40 pm. All procedures were recorded, graded, and reviewed by a board-certified internist (J. Byron). Procedures were subjectively scored from 1 to 5 (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) for the following categories and combined to create a procedural difficulty score: difficulty accessing urethra, difficulty passing the cystoscope through the urethra, difficulty accessing the urinary bladder, and iatrogenic changes made to the urinary structures during the procedure. Procedure duration and the number of times the cystoscope was inserted and removed were recorded. Dogs were housed in hospital treatment wards overnight after cystoscopy, and an overnight ward technician (K. Fields) observed the dogs hourly and recorded the number and times the dogs urinated as well as other behavioral and pain indicators.

During hospitalization, 2 scales were used to measure analgesia by 1 of 2 of the authors (L. Rayhel, L. Harjes) blinded to the epidural status of the patient. All intradog assessments were performed by the same investigator. All assessments were performed using numerical rating pain scales (NRS), a modified Melbourne Pain Scale (MPS), as well as a numerical rating sedation scale performed the morning of procedure, 4 to 6 hours postprocedure, 10 pm postprocedure, and 24 hours postprocedure (Supplemental File 1).⁵⁻⁸ Temperature, pulse, and respiration rates also were obtained at each time point. These data were used as outlined in the MPS. At any time point, if an animal had a NRS pain score >4 or a MPS score >12, that dog would be given rescue analgesia as needed and withdrawn from the study. After discharge from the hospital, owners were required to complete the same NRS pain scale, NRS sedation scale, a NRS pruritus scale, as well as additional NRS scales to assess comfort at home 5 days postdischarge (Supplemental File 2). The preprocedural pain, pruritus, and sedation scores were used as a baseline for comparison.

A complete neurologic examination was performed before study enrollment. A targeted neurologic examination was recorded for each dog the morning of and the morning after cystoscopy. Recordings were reviewed retrospectively by a board-certified neurologist who was blinded to epidural status (L. Cook). Recordings of the neurologic examinations included gait evaluation, evaluation of hindlimbs, as well as perineal reflexes. Neurologic evaluations were deemed normal or abnormal at both time points for each individual dog. The morning after cystoscopy, ultrasonographic bladder measurements were recorded as previously described before and after urination to assess urine retention unless urinary incontinence, refusal to urinate, or premature urination prevented this measurement.⁹ Postvoiding urine retention was defined as residual urine volumes ≤ 0.4 mL/kg.^{10,11} Dermatologic reactions at the site of the epidural or sham puncture were monitored during the anesthetic period, hospital recovery period, and after discharge.

Data were tested for normality using the D'Agostino Pearson test. Normally distributed data are reported as mean and standard deviation and nonnormally distributed data as median and range. Descriptive statistics are reported for the entire data set. Unpaired *t* test and Mann-Whitney *U* test were used to compare data between groups. Repeated measures variables (NRS pain, MPS, and NRS sedation) were compared using the Friedman test and Dunn's multiple comparisons test. Categorical variables, including the proportion of dogs in each group that had $\geq 50\%$ increase in pain scores after baseline, were compared using Fisher's exact test. For all analyses, values of $P \leq .05$ were considered significant. Standard statistical software was used (GraphPad Prism and Stata V11.0).

3 | RESULTS

Twenty-six dogs met all inclusion criteria and were prospectively enrolled in the study. From this population, 4 were removed from the study because of status unblinding, lack of patient cooperation, or incomplete follow-up. All dogs removed from the study were in the epidural group. Nine dogs in the epidural group and 13 dogs in the

nonepidural group completed the study. Five dogs were male, none of which was intact. Seventeen dogs were female, of which 9 were intact. Median age of all study dogs was 1.25 years (range, 0.42-10.9 years). Median body weight of all study dogs was 18.1 kg (range, 3.7-63 kg).

Within the group that received epidurals, 3 dogs were evaluated for urinary incontinence suspected to be secondary to congenital urinary sphincter mechanism incompetence (1 of which received intramucosal collagen injections), 3 dogs underwent laser ablation of ectopic ureters, 2 dogs underwent biopsy for diagnosis of urothelial cell carcinoma, and 1 dog (male castrated) underwent basket retrieval of urethroliths and voiding urohydropulsion. Within the group that did not receive epidurals, 5 dogs underwent laser ablation of ectopic ureters, 4 dogs underwent cystoscopy for evaluation of urinary incontinence unrelated to ureteral ectopy, 2 dogs (1 male castrated and 1 female spayed) underwent basket retrieval of urethroliths, 1 dog underwent cystoscopy for evaluation of recurrent urinary tract infections, and 1 dog was evaluated for persistent vulvar discharge (ultimate diagnosis of vaginitis). Four dogs, 1 in the epidural and 3 in the nonepidural group, had vaginal septae treated by laser ablation or manually broken down during the procedure.

No differences were identified in age, sex, body weight, procedure time, number of cystoscope passages, and procedural difficulty between epidural and nonepidural groups (Table 1). No differences were identified in the number of dogs in each group evaluated by each investigator assessing pain and sedation scores. Rescue analgesia was not required in any of the enrolled dogs at any time point.

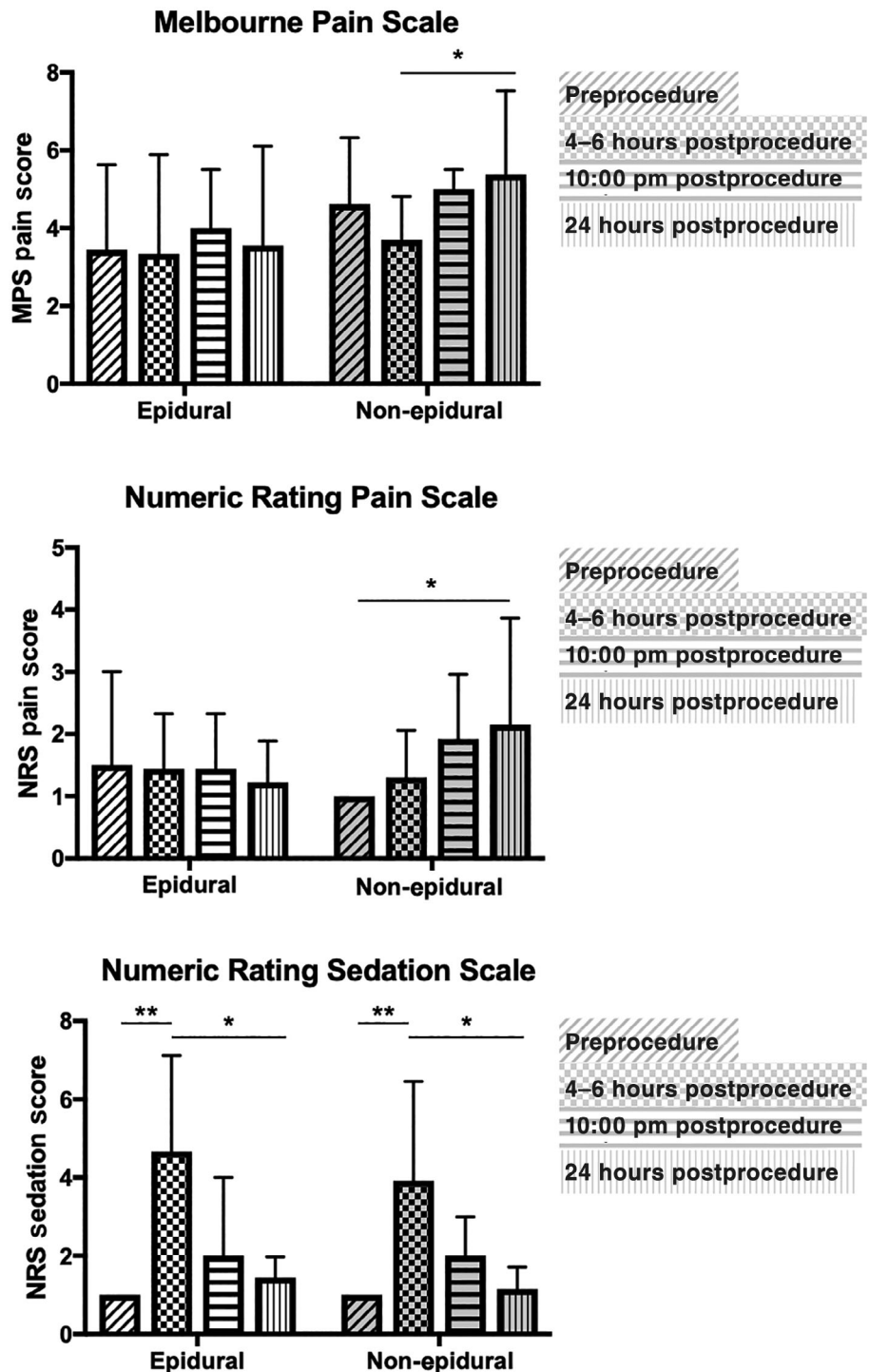
The MPS pain scores, NRS pain scores, and NRS sedation scores are presented in Figure 1. No differences were found in MPS pain scores over time in the epidural group ($P = .55$). Significant differences were identified in MPS pain scores over time in the nonepidural group ($P = .05$). No differences in NRS pain scores over time were observed in the epidural group ($P = .8$). Significant differences in NRS pain scores over time were identified in the nonepidural group ($P = .02$). Significant differences in NRS sedation scores over time were identified in both the epidural group ($P < .001$) and in the nonepidural group ($P < .001$). The proportions of dogs that had a $\geq 50\%$ increase in MPS ($P = .38$) or NRS ($P = .2$) pain scores after the procedure were not significantly different between the epidural and nonepidural groups. No differences were found in the results of 5-day postprocedure assessments by owners using the NRS pain, NRS sedation, or 13 NRS quality of life questions between the epidural and nonepidural groups. The results of statistical testing on 5-day postprocedure assessments are presented in Supplemental Table 1.

Pruritus was assessed at all time points in the study. No statistically significant differences were observed in pruritus between groups at any time point. At the preprocedural assessment, 1 dog in the non-epidural group had signs of pruritus. During hospitalization, at 4 to 6 hours post-, 10 pm post-, and 24 hours postprocedure, 1 dog in the epidural group and 2 dogs in the nonepidural group had signs of pruritus. At the day 5 owner assessment, 3 dogs in the epidural group and 6 dogs in the nonepidural groups had signs of pruritus. Additional adverse dermatologic effects were not observed in any dogs during the course of the study. Postprocedure urination variables intended

TABLE 1 Descriptive data and comparisons between the epidural and nonepidural group. *P* values less than .05 were considered statistically significant

Variable	Epidural group (n = 9)	Nonepidural group (n = 13)	<i>P</i> value
Sex	(33.3% male, 66.7% female)	(33.3% male, 66.7% female)	.61
Age	2.6 years (0.42-10.9)	0.96 years (0.42-8)	.33
Body weight	17.6 kg (7.3-63)	19.6 kg (3.7-48)	.73
Procedure time	29 minutes (18-60)	30 minutes (15-80)	.93
Number of scope passages	6 passages (2-12)	8 passages (5-20)	.11
Procedural difficulty score	4 (4-8)	6 (4-10)	.27

FIGURE 1 Graphical representation of Melbourne Pain Scale (MPS) scores, numerical rating pain scales (NRS) scores, and NRS sedation scores in both the epidural and nonepidural groups. Data are presented as median and interquartile range. (*The *P* value is less than or equal to .05; **The *P* value is less than or equal to .01.)



	Epidural	Nonepidural	P value
Time to first urination	8.32 hours ± 6.19	5.06 hours ± 3.66	.13
Postvoiding urine volume	0.43 mL/kg (0.06-12.31)	0.31 mL/kg (0.01-3.89)	.33
Number of urinations	5 (1-11)	3 (2-10)	.72

TABLE 2 Descriptive data and comparisons between the epidural and nonepidural group for outcomes related to urinary retention. *P* values less than .05 were considered statistically significant

to monitor for urine retention were not significantly different between epidural and nonepidural groups. Results of the postprocedure urination findings are presented in Table 2. Five dogs in the epidural group and 6 dogs in the nonepidural group had postvoiding residual urine volumes >0.4 mL/kg. Frequency of urine retention the morning after the procedure was not significantly different between groups ($P = .96$). A single dog in the epidural group had much higher urine retention volume (12.3 mL/kg) than the remaining dogs in the epidural group (all other postvoiding urine retention volumes were ≤ 3.1 mL/kg). No change in neurologic status was observed in any study animal before or after the epidural. Neurologic evaluations were only available for review in 13 of the study dogs (7 nonepidural, 6 epidural) because of lost video recording data before evaluation.

4 | DISCUSSION

Clinical experience in human medicine indicates that pain and discomfort are associated with cystoscopy.³ As such, there is widespread support for the possibility that cystoscopy in dogs also may cause discomfort and pain that should be managed appropriately.¹ Despite the ongoing need for an optimized pain management approach in lower urinary endoscopy in veterinary medicine, no consensus currently exists on which protocol is best. In our study, epidural analgesia was added to a routine anesthetic protocol to potentially improve postprocedural pain management. Using the MPS and NRS pain scale, the dogs that did not receive epidural analgesia were noted to have poor pain control after the procedure. This conclusion was supported by significant differences in serial MPS and NRS pain scale scores in postprocedural assessments of the nonepidural group. No significant differences were observed in the MPS and NRS pain scores in the dogs in the epidural group.

Subjective measures to evaluate pain, such as NRS, allow the user to assign a value (physical or theoretical) to the degree of pain that an animal appears to be experiencing.^{12,13} These systems also can be used to assign a point value to other patient characteristics, such as pruritus, sedation, mentation, or agitation as was done in our study.⁶ Scores were assigned to each patient at baseline, before the cystoscopy procedure, and then repeatedly thereafter by the same observer. Using this system, we detected differences in both pain control and sedation scoring throughout the duration of the study. The NRS scoring system was chosen for our study because it has been shown to correlate with other pain assessment methodologies in human medicine and the NRS scale is a readily applicable format that is not specific to a single disease process or procedure.¹⁴⁻¹⁷ For these reasons, the NRS scale is utilized frequently in veterinary medicine, because targeted or validated scoring

systems are not available for specific scenarios, including lower urinary tract discomfort. The flexibility of these methods however is derived from the fact that they rely on clinical observation and judgment to determine an impression of pain, which is associated with some drawbacks.

Relying purely on clinical assessments for scoring pain has limitations as a consequence of high interindividual variability in scoring as well as subjectivity in scoring.¹⁸ In clinical practice, veterinarians rely on behavioral assessments and the practitioner's perception of how noxious stimuli affect each patient to determine whether pain exists and whether it has been managed appropriately. A key point in this approach is the concept that pain is a state of perception, and it cannot completely and accurately be modeled from visual observation of behaviors alone. Unfortunately, in veterinary species, it is impossible to obtain a direct report on the perception of pain in an individual animal.¹³ When studies in human medicine have examined the accuracy of pain assessment by third party observations, it has been shown that these conclusions often can be incongruent with pain perception by the patient.¹⁹ In veterinary medicine, the misinterpretation of animal behavior and affect during pain assessment has been shown to result in inadequate pain management protocols.²⁰ We attempted to limit interindividual variability by having all scoring performed by the same individual, but subjectivity in the system still remains. Furthermore, after discharge from the hospital, we relied on owner observation and scoring for some of our results. Owners are not trained in animal behavior or clinical pain assessment. Clinicians frequently rely on owner reports of animal comfort after discharge, however despite modeling a clinical scenario, the potential for inaccuracy among owner assessments is an important limitation in our study. Therefore, despite the fact that the NRS system worked well in our study, a more robust clinical pain scoring scheme for use in veterinary medicine still is needed.

To improve the accuracy of subjective visual assessments, numerous studies in veterinary medicine have attempted to use behavior and other clinical indicators to quantify pain in companion animal patients using specific scoring systems.¹³ Quantification schemes for pain can be subjective, semiobjective, or objective. Unfortunately, fully objective measures of pain in both human and veterinary patients are impractical and not easily clinically applied. However, semiobjective measures of pain can be readily applied to veterinary patients and may produce more reliable and repeatable measures than simple clinical evaluation. The MPS assigns point values to specific behaviors and postures as well as using changes in vital signs such as heart and respiration rates and body temperature to assign an overall semiobjective pain score to an animal.⁵ This scale was developed specifically for pain associated with abdominal surgery, but since has been modified for other procedures similar to what was done in our study.⁵ The MPS scores detected

significant differences in pain control in the nonepidural dogs in our study. This finding provided further evidence that pain control was poor in the postoperative period for dogs not receiving epidurals. Future studies should be conducted to develop even more specific pain assessment schemes for reliable semiobjective assessments of lower urinary tract discomfort.

The ability to assess pain accurately in veterinary studies is a major limitation to all pain control research.¹³ The methods used for pain assessment in our study are not objective and prone to error, despite being the most readily available option for clinical veterinary research. More robust and heavily validated pain assessment methods should be developed for future use and reassessment of the effects of epidurals. However, even with the limitations of pain assessment in veterinary medicine, our data indicate poor pain control in the absence of an epidural during lower urinary tract endoscopy. Additionally, in our study, there was no evaluation of the specific anesthetic requirements intraoperatively because of variability in anesthetists during the anesthetic maintenance phase. The addition of an epidural may have decreased intraoperative anesthetic requirements by pain and sensation reduction. Future studies should evaluate the effects of the epidural treatment on intraoperative pain management.

The epidural procedure was well-tolerated without major complications in any cases. Potential minor complications including urine retention, dermatologic reactions, and pruritus were not different between dogs that received epidurals as compared with those that did not. Residual neurologic deficits were not present the morning after the epidural, and no major neurologic complications were noted in any dog. One dog experienced urine retention the morning after the procedure, but the dog did not have clinical signs or any documentation of urine retention 6 months after the conclusion of the study, based on the medical record. Based on this dog, additional studies should focus on both the short- and long-term effects of epidurals on urine retention in dogs with lower urinary tract disease. This information would better allow clinicians to weigh the benefits of pain alleviation against the risk of urine retention in clinical patients. The low frequency of adverse effects in our study is similar to previous reports on epidural use in small animals in veterinary medicine.²¹ Our findings add to the literature supporting epidurals as a safe intervention when performed correctly for an indicated reason. Based on these findings, epidurals appear to be a well-tolerated addition to the anesthetic regimen used during cystoscopy.

Many factors affect the spread of drug in the epidural space, including volume and concentration of drug, speed and pressure during injection, site of induction, direction of the needle bevel, position of the animal, size and permeability of the intervertebral foramina, amount of fat in the epidural space, size of the associated venous and lymphatic plexes, age and physical condition, and baricity and specific gravity of the injected solution.²¹⁻²⁴ Some studies have identified farther cranial spread than initially expected from administration of 0.2 mL/kg at the lumbosacral epidural space, with spread extending as high as the C6 vertebra.²⁴ The drugs selected for our study were chosen to provide analgesia in the postprocedural period with sensory effects and without motor blockade. The calculated volume,

considering the drug concentrations and dosages in our study, resulted in volumes between 0.20 and 0.22 mL/kg. The innervation of the bladder is complex and involves both sympathetic and parasympathetic input from visceral efferent neurons. Sympathetic preganglionic cell bodies are located in the lateral horn of L1-L4 spinal cord segments (primary function in urine storage) and the parasympathetic preganglionic cell bodies are located in the lateral horn of the sacral spinal cord segments. The postganglionic cell bodies are excitatory to the detrusor muscle causing contraction and bladder evacuation. The low end of the volume of 0.2 mL/kg should be appropriate, given the goal of an effect on bladder evacuation in our study.

Our study had several limitations. Sex of the dogs was not controlled, which could have biased pain results because more manipulation of the cystoscope instrument within the urethra would be expected in male dogs. However, no difference in sex was identified between epidural and nonepidural groups. Additionally, underlying conditions or reasons for performing cystoscopy also were not controlled in the study. This factor may have impacted pain scores between groups, because certain underlying conditions may be inherently more painful, and the need for secondary procedures associated with cystoscopy differs among conditions. For example, there were differences between groups including more dogs receiving laser ablation in the non-epidural group and a single dog in the nonepidural group that had 20 passages through the urethra. These factors may have affected our results. The number of animals in our study is also a limitation and may have resulted in portions of the study being underpowered, thus increasing the risk of type II statistical error in the results of some of the variables evaluated. Most notably, this factor includes limiting the ability to analyze postprocedural pain according to specific disease category and procedure type. Additional studies within disease and procedure categories are needed to better determine the efficacy of epidural at alleviating postprocedural pain in specific clinical situations.

Furthermore, our study experienced a substantial drop out of animals that were not accounted for in an intention-to-treat analysis, which could help evaluate the impact of the missing data on the results. The groups in our study were randomized to avoid bias initially, but the inability to analyze the 4 dogs that dropped out of the epidural group during the study may have affected the benefits of the randomization. Specifically, multiple imputation, maximum likelihood, or sensitivity analyses would improve confidence in the results of our study on the effects of epidurals in conjunction with general anesthesia for cystoscopic procedures. Additionally, dogs with conditions that would be expected to cause baseline cystitis or urethritis (eg, urinary tract infections, urethroliths) were included, and this factor was not controlled for in the study. Baseline pain and pruritus scores however were not different between groups, and thus potentially preprocedure cystitis or urethritis did not affect our results.

5 | CONCLUSIONS

Many dogs undergoing cystoscopy experience discomfort and pain during the procedure and in the immediate postprocedure period.

We failed to identify a difference in the proportion of dogs exhibiting a pain control benefit of epidural anesthesia in comparison to nonepidural anesthesia. However, dogs not receiving epidural anesthesia had significantly different pain scores during the initial postprocedural period. Additional studies are required to better assess epidural effects on anesthetic requirements intraoperatively using more advanced pain measurement techniques with the goal of optimizing pain management protocols for dogs undergoing cystoscopy.

ACKNOWLEDGMENT

No funding was received for this study.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the IACUC at The Ohio State University.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Rayhel LH, Harjes LM, Aarnes TK, et al. Short-term efficacy of epidural pain management in dogs undergoing cystoscopy. *J Vet Intern Med.* 2021;35:980-986. <https://doi.org/10.1111/jvim.16055>