

Incidence of and risk factors for seizures after myelography performed with iohexol in dogs: 503 cases (2002–2004)

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Objective—To establish the incidence of and risk factors for seizures following myelography performed with iohexol in dogs.

Design—Retrospective case series.

Animals—503 dogs.

Procedures—Medical records were searched for dogs that underwent myelography between April 2002 and December 2004. Data extracted included body weight, breed, age, sex, volume and dose of iohexol, site of injections, location of lesion, duration of anesthesia, surgical procedures immediately after myelography, use of acepromazine, and presence or absence of seizures.

Results—15 (3%) dogs had postmyelographic seizures. Risk factors significantly associated with seizures were size of dogs (large dogs were 35.35 times as likely to have seizures as were small dogs), location of contrast medium injection (dogs in which iohexol was injected into the cerebellomedullary cistern were 7.4 times as likely to have seizures as were dogs in which iohexol was injected into the lumbar cistern), location of lesion (dogs with lesions at the level of the cervical portion of the vertebral column were 4.65 times as likely to develop seizures as were dogs with lesions in other regions), and total volume of iohexol. Mean \pm SD total volume of iohexol was 11.73 ± 5.52 mL (median, 10.5 mL [range, 3.0 to 21.0 mL]) for dogs that had seizures and 4.57 ± 4.13 mL (median, 3.5 mL [range, 0.75 to 45.0 mL]) for those that did not.

Conclusions and Clinical Relevance—Large-breed dogs with cervical lesions and large volumes of iohexol injected into the cerebellomedullary cistern had the highest risk of seizures. The use of contrast medium volumes > 8 mL in large dogs should be avoided, with preference given to injections into the lumbar cistern. (*J Am Vet Med Assoc* 2011;238:1296–1300)

Myelography is a common neuroimaging technique used in the diagnosis of spinal cord disorders in dogs and cats. Although myelography is generally believed to be a safe diagnostic procedure, several complications can occur. Complications associated with myelography in animals include deterioration of the patient's neurologic status, penetration of the cervical spinal cord or brainstem, injection of the contrast agent into the spinal cord, vomiting, apnea, asystole, focal or generalized seizures, and death.^{1–6}

To minimize the neurotoxic effects associated with myelography, the ideal contrast agent should be pharmacologically inert, miscible with CSF, water soluble, and radiopaque at an isotonic concentration.^{5,7,8} Metrizamide, a first-generation nonionic contrast agent, is no longer used because of the numerous adverse effects

ABBREVIATIONS

CI	Confidence interval
CSM	Cervical spondylomyelopathy
IVDD	Intervertebral disk disease

associated with its neurotoxicity.^{5,7,9,10} The incidence of postmyelographic seizures associated with the use of metrizamide was between 15% and 65%.^{11,12} Because of the high risk of postmyelographic seizures with the use of metrizamide, second-generation nonionic contrast agents such as iopamidol and iohexol were introduced, followed more recently by newer contrast agents such as iotrolan and iomeprol.^{5,13–15} Among all contrast media for myelography in dogs, iohexol appears to be the most commonly used. As for its predecessor, metrizamide, the use of iohexol for myelography is associated with seizures. The frequency of postmyelographic seizures with iohexol was believed to be relatively low, occurring usually in $< 10\%$ of dogs that underwent a myelographic procedure.^{4,8,16} However, a more recent study³ with the largest patient population studied to date found that 21.4% of dogs that had undergone myelography with iohexol had at least 1 seizure.

As our experience at the Ontario Veterinary College appeared different, we set out to investigate the incidence and risk factors of postmyelographic seizures in a large canine population. Even though some disease

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Supported by the Ontario Veterinary College, University of Guelph. Presented in part as an oral presentation at the 27th Forum of the American College of Veterinary Internal Medicine, Montreal, June 2009.

The authors thank Ms. Aleisha Lusk and Gabrielle Monteith for assistance with data collection and statistical analyses.

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conditions appear to be associated with a higher incidence of postmyelographic seizures,¹⁷ we hypothesized that the overall incidence of postmyelographic seizures would be < 5%.

Materials and Methods

Criteria for selection of cases—The medical and radiology records of the Ontario Veterinary College Veterinary Teaching Hospital were searched for dogs that had undergone myelography between April 2002 and December 2004. Terms used in the search were myelography, myelogram, contrast, spine, and spinal. Criteria for inclusion in the study were cervical or lumbar myelography and medical records with sufficient detailed information for data collection. The exclusion criteria were incomplete medical records and a history of epilepsy.

Procedures—Myelography was performed in all dogs studied by use of iohexol at a concentration of 240 mg of iodine/mL injected into the cerebellomedullary cistern, lumbar cistern, or both. Injections into the lumbar cistern were preferred for dogs with lesions in the lumbar, thoracolumbar, and thoracic regions, whereas injections into the cerebellomedullary cistern were more commonly performed in dogs with lesions at the level of the cervical portion of the vertebral column. Premedication for anesthesia was achieved with an opioid (hydromorphone, oxymorphone, or morphine), diazepam, or acepromazine, and anesthesia was induced with propofol (IV) and maintained with isoflurane.

The following information was compiled from the medical records: breed, sex, age, body weight, volume and dose of iohexol injected, site and number of injections, final diagnosis, location of the lesion, duration of anesthesia, time from injection to anesthetic recovery, whether surgery immediately followed myelography, and whether seizures were observed and, if they were, the type and number of seizures. The duration of anesthesia was defined as the time from intubation to extubation. The use of acepromazine was also recorded and analyzed. The time from injection to anesthetic recovery was defined as the time from the initial injection of iohexol until extubation. Seizures were classified as either generalized or focal, depending on whole body or facial involvement. The lesions were classified into 3 categories: IVDD, CSM, and others (eg, spinal cord tumors, fibrocartilaginous embolic myelopathy, degenerative myelopathy, fracture, luxation, lumbosacral syndrome, and spinal cord cysts).

Statistical analysis—Variables (breed, sex, body weight, dose and volume of iohexol, site and number of iohexol injections, surgery following the myelography, duration of anesthesia, time from injection to recovery, final diagnosis, and lesion location) were compared between dogs that did and did not have postmyelographic seizures. For analysis, the dogs were categorized as either small (≤ 9 kg [19.8 lb]), medium (> 9 and ≤ 20 kg [44 lb]), or large (> 20 kg). Analysis was performed by use of univariate exact conditional analysis of possible predictors of postmyelographic seizures. Fisher exact tests for binary predictors were used to evaluate the relationship between the development of seizures

following a myelography and several different risk factors (breed, sex, size of dog, site of injection of iohexol, number of injections, whether the dog underwent surgery following myelography, final diagnosis, location of lesion, and use of acepromazine). Logistic regression with exact conditional tests was used to test for several variables (size of dog, site of injection, volume, dose, duration of anesthesia, time from injection of iohexol until recovery, final diagnosis, and location of lesion). Analyses were performed by use of statistical software.^a Significance was established at values of $P < 0.05$.

Results

In total, 583 dogs were identified during the study period. Eighty dogs were excluded because the medical records were incomplete. Five hundred three dogs met the inclusion criteria and were studied. Sixty-four different dog breeds were represented in the study, with 204 females and 299 males. The breeds represented included Dachshund ($n = 117$), mixed-breed dog (74), Shih Tzu (29), Doberman Pinscher (24), Jack Russell Terrier (21), Beagle (20), Bichon Frise (18), Cocker Spaniel (17), Labrador Retriever (12), Cock-a-poo (11), Lhasa Apso (10), German Shepherd Dog (10), Pekingese (10), Pomeranian (10), Yorkshire Terrier (8), Rottweiler (7), Basset Hound (6), Poodle (6), Chihuahua (5), Dalmatian (5), Miniature Poodle (5), Golden Retriever (5), Great Dane (4), Siberian Husky (4), Pug (4), Soft Coated Wheaten Terrier (3), Toy Poodle (3), and Coton du Tulear (3). Thirty-six other breeds were represented by 1 or 2 dogs each. The age of dogs ranged from 1 to 16 years (median, 7 years; mean \pm SD, 6.82 ± 2.93 years). Body weights ranged from 1.20 to 89.0 kg (2.64 to 195.8 lb) with a median body weight of 9.7 kg (21.3 lb) and mean \pm SD body weight of 15.83 ± 13.53 kg (34.826 ± 29.766 lb). The total volume of iohexol administered ranged from 0.75 to 45 mL (median, 3.5; mean \pm SD, 4.83 ± 4.39 mL). The total dose of iohexol administered ranged from 0.1 to 2.2 mL/kg (0.05 to 1 mL/lb) with a median of 0.33 mL/kg (0.15 mL/lb) and mean \pm SD of 0.35 ± 0.25 mL/kg (0.159 ± 0.114 mL/lb). The duration of anesthesia (time from intubation to extubation) ranged from 1.2 to 10.5 hours (median, 3.5 hours; mean \pm SD, 3.61 ± 1.24 hours). The time from injection of iohexol to the time of extubation ranged from 0.5 to 8.25 hours (median, 2.5 hours; mean \pm SD, 2.48 ± 1.19 hours).

Fifteen (3%) dogs had postmyelographic seizure activity. The breeds represented by these 15 dogs included Doberman Pinscher ($n = 5$), Rottweiler (3), and 1 each of Jack Russell Terrier, Dachshund, Poodle, Dogue de Bordeaux, Great Dane, Bernese Mountain Dog, and mixed-breed dog. There were 9 males and 6 females. Of the 15 dogs, 7 had 1 generalized seizure, 6 had focal seizures, and 2 had both generalized and focal seizures. The seizures stopped spontaneously or were managed with diazepam (IV), except in 1 dog that had to receive propofol (IV) to control the seizure activity. Twelve of the 15 dogs that had postmyelographic seizures had received > 8 mL of iohexol. A comparison of the age, body weight, total volume of iohexol administered, dose of iohexol, duration of anesthesia, and time from iohexol injection to extubation between dogs that

had postmyelographic seizures and those that did not was made (Table 1).

Of the 503 dogs, 140 (27.8%) were classified as large dogs, 124 (24.7%) as medium dogs, and 239 (47.5%) as small dogs. In the large dog group, 13 of 140 (9.3%) dogs had postmyelographic seizure activity. Seizures were seen in only 2 of 124 (1.6%) medium dogs, and none of the small dogs ($n = 239$) had seizures. Large dogs had a significantly ($P < 0.001$) higher risk of seizures, compared with small dogs, and were found to be 35.35 times as likely to have a seizure as were small dogs (95% CI, 5.82 to infinity). Similarly, there was a significant ($P = 0.009$) difference in the development of seizures between large and medium dogs. Large dogs were found to be 10.07 times as likely to have a postmyelographic seizure, compared with medium dogs (95% CI, 1.47 to 434.94).

There was a significant ($P < 0.001$) difference between the likelihood of seizures in Doberman Pinschers and in the other 63 breeds of dogs represented in the study. Of the 24 Dobermans included in the study, 5 (20.8%) were observed to have postmyelographic seizures, compared with 10 of the 479 (2.1%) dogs of other breeds. Doberman Pinschers were found to be 12.34 times as likely to have a postmyelographic seizure as were dogs of the other breeds (95% CI, 3.84 to 39.66). Rottweilers also had a significantly ($P < 0.001$) higher seizure risk than did other breeds. Of the 7 Rottweilers included in the sample, 3 had postmyelographic seizures. In this study, Rottweilers were 30.25 times as likely to have a postmyelographic seizure as were dogs of any other breed, including Doberman Pinschers (95% CI, 6.09 to 150.25).

Data for site of injection of the contrast agent were analyzed by comparison of the development of seizures associated with injections into the lumbar or cerebellomedullary cistern. A total of 486 dogs had contrast agent injected into either of these sites. Dogs ($n = 17$) that had injections into both cisterns were not included in the data analysis. Of the 424 dogs that had injections into the lumbar cistern, 6 (1.4%) had a postmyelographic seizure. Six of the 62 (9.7%) dogs that had injections into the cerebellomedullary cistern had a seizure. The dogs that had injections into the cerebellomedullary cistern had a significantly ($P < 0.001$) higher risk of seizures and were 7.46 times as likely to develop a seizure as were those dogs that had injections into the lumbar cistern (95% CI, 2.32 to 23.94).

The number of injections was analyzed for a relationship with the development of seizures, regardless of where the injections were made. Of 36 dogs that received

> 1 injection of iohexol, 3 (8.3%) had a postmyelographic seizure. On the other hand, 12 of 467 (2.5%) dogs that received a single injection had a seizure. Dogs that received > 1 injection of iohexol did not have a significantly ($P = 0.08$) higher incidence of postmyelographic seizures than did those dogs that were injected once.

There was a significant ($P < 0.001$) relationship between the volume of iohexol injected and the development of seizures. For each 1-mL increase in the volume of iohexol, the probability of seizure was 1.2 times as likely (95% CI, 1.11 to 1.32). On the other hand, there was no significant ($P = 0.689$) relationship between the dose per kilogram of iohexol administered and the development of postmyelographic seizures.

For dogs that did not have surgery following myelography, there was a significantly ($P < 0.001$) higher incidence of seizures than for those that did have surgery. Of the 145 dogs that recovered without surgery, 12 (8.3%) had a seizure, but of the 358 dogs that had surgery after myelography, only 3 (0.84%) had seizures. If no surgery was performed following myelography, these dogs were 10.67 times as likely to have a seizure as were dogs that did have surgery (95% CI, 2.97 to 28.43). No significant ($P = 0.314$) relationship was found between duration of anesthesia and occurrence of seizures. Even though the time from injection of iohexol to recovery (extubation) was also not significant ($P = 0.056$), it was a more relevant parameter than the total duration of anesthesia. For every hour that the length of time decreased from injection of iohexol to anesthetic recovery, the risk of developing a seizure was 2.61 times as likely (95% CI, 0.99 to 7.50).

A relationship was found between the level of lesion and the development of seizures. Of the 104 dogs with cervical lesions, 8 (7.7%) had a seizure. Three of 139 (2.16%) dogs with lesions in the thoracic region, 3 of 99 (3.03%) dogs with lesions in the thoracolumbar region, and none of 128 dogs with lesions in the lumbar region had a seizure. A significant ($P = 0.005$) relationship was found when lesions at the level of the cervical portion of the vertebral column were compared with lesions at all other levels. Dogs with a cervical lesion were 4.65 times as likely to have a seizure, compared with dogs with a lesion in any other region (95% CI, 1.43 to 15.46). Among the 8 dogs with cervical lesions, 6 had injections into the cerebellomedullary cistern, 1 in the lumbar cistern, and 1 in both. Among the 6 dogs with lesions in the thoracic or thoracolumbar region, 5 had injections in the lumbar cistern and 1 in both the lumbar and cerebellomedullary cistern.

In terms of diagnoses, the dogs were placed into 3 groups: those with IVDD, those with CSM, and those

Table 1—Comparison of dogs that did and did not have postmyelographic seizure activity after iohexol injection.

Variable	Dogs with seizures		Dogs without seizures	
Age (y)	7.07 ± 2.19	7.0 (3–12)	6.81 ± 2.95	7.0 (1–16)
Body weight (kg)	36.58 ± 14.73	38.4 (9.4–65.0)	15.12 ± 12.90	9.7 (1.20–89.00)
Total volume of iohexol (mL)	11.73 ± 5.52	10.5 (3.0–21.0)	4.57 ± 4.13	3.5 (0.75–45.00)
Total dose of iohexol (mL/kg)	0.33 ± 0.10	0.31 (0.14–0.59)	0.35 ± 0.25	0.33 (0.08–3.90)
Duration of anesthesia (h)	3.30 ± 0.93	3.25 (2.25–5.5)	3.62 ± 1.25	3.5 (1.20–10.50)
Time from iohexol injection to extubation (h)	1.9 ± 0.65	2.0 (1.00–2.75)	2.50 ± 1.20	2.5 (0.50–8.25)

Data are reported as mean ± SD and median (range).
To convert mL/kg to mL/lb, divide by 2.2.

with other conditions. Of the 364 dogs diagnosed with IVDD, 3 (0.8%) had seizures. Seven of the 28 (25%) dogs diagnosed with CSM had postmyelographic seizures. Of the 111 dogs with a diagnosis other than that of IVDD or CSM, 5 (4.5%) had seizures. Dogs diagnosed with CSM were significantly ($P < 0.001$) more likely (40.1 times as likely) to have postmyelographic seizures as were dogs with IVDD.

The relationship between acepromazine and postmyelographic seizures was investigated. Six of the 15 dogs that had a seizure had received acepromazine: 4 as preanesthetic medication and 2 upon recovery. Of 488 dogs that did not have postmyelographic seizures, 139 (28.4%) received acepromazine. Acepromazine was used before anesthesia induction in 33 dogs, upon recovery in 97, and before induction and upon recovery in 9. No relationship was identified between the use of acepromazine and postmyelographic seizures ($P = 0.38$; odds ratio, 1.67 [95% CI, 0.58 to 4.9]). The sex of the dogs also did not have a significant ($P = 1.00$) impact on the development of seizures. Six of 204 (2.94%) female and 9 of 299 (3%) male dogs had a seizure.

Discussion

This study was aimed at identifying the incidence of postmyelographic seizures in a large canine population and the risk factors associated with it. The incidence of seizures in our study was low, with only 15 of 503 (3%) dogs developing postmyelographic seizures. Several factors were associated with a higher risk of postmyelographic seizures, such as the size of the dog, site of the injection, total volume of iohexol injected, and location of the lesion.

The total volume of iohexol appears to be a key factor to explain the significantly lower incidence of seizures in our study, compared with the study by Barone et al.³ In our study, the mean total volume of iohexol injected was 4.5 mL in dogs that did not have a seizure and 11.7 mL in dogs that did have a seizure. Conversely, in the Barone et al³ study, where seizures were observed in 21.4% of dogs, the mean total volume of iohexol injected was 9.1 mL in dogs that did not have a seizure and 16.8 mL in dogs that did have a seizure. Both studies used iohexol at the same concentration (240 mg/mL). There are different concentrations of iohexol available for myelography in veterinary medicine (180 to 350 mg/mL).^{3,4,8,13,16,18} Even though this has not been extensively studied, the concentration of contrast medium does not appear as important as the total volume.⁸ In a study¹⁸ with 68 dogs, where myelography was performed with iohexol at concentrations of 300 and 350 mg/mL, the authors found no postmyelographic seizures in their population. In that study, the maximum volume of iohexol injected was 8 mL, with a mean total dose of 5.7 mL in large dogs. In our study, 12 of the 15 dogs that had seizures received > 8 mL of iohexol. The previous findings, combined with ours, suggest that the total volume is more important than the contrast medium concentration and that an upper limit of 8 mL is indicated. Even though higher concentrations of iohexol appear to be safe, it is generally recommended to use iohexol at concentrations of 180 or 240 mg/mL.⁵

Similar to the findings of Barone et al,³ the dose of contrast medium was not a significant risk factor, even though the dose used in both studies was quite different. The mean dose administered in our study was 0.35 mL/kg, which is within the recommended range of 0.3 to 0.45 mL/kg (0.14 to 0.205 mL/lb),^{5,7} whereas in the Barone et al³ study, where 21.4% of dogs had a seizure, a dose of 0.58 mL/kg (0.264 mL/lb) was used. Other studies reported doses of 0.3 to 0.5 mL/kg (0.14 to 0.23 mL/lb) with 10% of dogs having seizures,⁴ 0.3 to 0.45 mL/kg with 7% of dogs having seizures,¹⁹ and 0.25 mL/kg with 1% of dogs having seizures.¹⁶ Because the total volume of iohexol injected was a significant risk factor for development of postmyelographic seizures while the dose was not, the total volume should dictate the amount of contrast medium to be used in small animal myelography. Further studies could investigate alternative methods to determine the optimal dose of contrast agent to inject (eg, by use of body surface areas). In the meantime, the authors recommend a maximal volume of 8 mL for myelography, even in large- and giant-breed dogs, reserving additional volumes in cases where the myelographic study is nondiagnostic.

We found that Doberman Pinschers and Rottweilers had a higher risk of postmyelographic seizures than did other breeds. One prior study⁴ suggested that Doberman Pinschers had a higher seizure risk, while another study³ did not find such an association. Based on our study, the higher incidence of seizures in these breeds is likely the result of the dogs' size and injection into the cerebellomedullary cistern. These breeds are predisposed to CSM, a risk factor for postmyelographic seizures previously identified in another study⁴ and confirmed in ours. Twenty-five percent of dogs with CSM had a seizure. Large-breed dogs, not just specifically Doberman Pinschers or Rottweilers, are more likely to have a number of factors that predispose them to the occurrence of seizures, including being diagnosed with CSM, injection into the cerebellomedullary cistern, and receiving a larger total volume of iohexol than do smaller breeds. In our study, 9.3% (13/140) of large dogs had a seizure, while only 1.6% (2/124) of medium dogs and none (0/239) of the small dogs had a postmyelographic seizure.

The incidence of seizures following myelography was also influenced by the site and number of injections of iohexol. Injection of iohexol into the cerebellomedullary cistern³ or multiple injections⁴ have been observed to increase the likelihood of postmyelographic seizures. In our study, seizures were 7.46 times as likely to occur in those dogs that had iohexol injected into their cerebellomedullary cistern, an odds ratio comparable to that described by Barone et al³ (ie, 6.9 times as likely). Multiple injections were not found to increase the risk of seizures. Because of the small number of dogs with seizures in our study, we could not assess the relationship between multiple injections and location of injection, but multiple injections, particularly in the cerebellomedullary cistern, have been associated with a higher seizure risk.⁴ As such, it is recommended to avoid multiple injections of contrast medium into the cerebellomedullary cistern.

Performing surgery immediately following a myelographic procedure increases the duration of anesthesia

and is proposed to be protective against the development of seizures.¹⁹ The findings of our study support this. Dogs not having surgery were 10.6 times as likely to have a seizure as were dogs that did have surgery. However, Barone et al³ found that surgery was only a significant factor on univariate analysis, while on multivariate analysis, surgery alone did not decrease the risk of seizures. The small number of dogs with seizures in our study did not allow testing for multivariate relationships. In another study,⁴ a relationship between surgery and decreased risk of postmyelographic seizures was not found.

In agreement with other studies,^{3,4,12,19} an association between duration of anesthesia (defined as the time from intubation to extubation) and incidence of postmyelographic seizures was not found (mean total duration of anesthesia was 3.3 hours for dogs with seizures and 3.6 hours in dogs without seizures). Even though the time from iohexol injection to recovery was also not significant ($P = 0.056$; mean, 1.9 hours in dogs with seizures versus 2.5 hours in dogs without seizures), this parameter may be clinically relevant. This, combined with the fact that surgery was significantly associated with a lower risk of seizures, indicates that the duration of anesthesia after iohexol injection is more important to minimize the risk of seizures than is the total duration of anesthesia, which includes the anesthesia time before iohexol injection. The type of and drugs used for anesthesia do not appear to have an influence on the development of seizures.^{4,12,18,19} We decided to specifically investigate the possible relationship between acepromazine and postmyelographic seizures because acepromazine is commonly believed to decrease the seizure threshold in dogs.²⁰ No significant association was found between the use of acepromazine either before or after iohexol injection and postmyelographic seizures. In another study,¹⁸ acepromazine was used in 68 dogs as a preanesthetic medication before myelography and seizures were not observed in any of the dogs. A recent study²⁰ also looked at the use of acepromazine in dogs with a history of seizures and found that acepromazine did not induce seizure activity in any of the dogs.

Even though Barone et al³ did not find a significant association between location of the lesion and seizures, in our study, dogs with lesions at the level of cervical portion of the vertebral column were 4.65 times as likely to have a seizure, compared with dogs with lesions in other regions.

Although several factors have been identified that increase the likelihood of postmyelographic seizures in dogs, these factors interact with one another and, as such, careful consideration must be used when planning a myelographic procedure. Previous studies^{4,8,12,16,18,21} examining the incidence of and risk factors for postmyelographic seizures in dogs had sample sizes that were comparatively small, ranging from 50 to 182 dogs. Our sample was substantially larger ($n = 503$), and only 15 (3%) dogs had seizures. This low incidence of seizures should reassure clinicians and dog owners that myelography is a relatively safe diagnostic procedure, given that certain factors are taken into account during the procedure. On the basis of our study, the risk of postmyelographic seizures for a small-breed dog with a thoracolumbar lesion having lumbar myelography would be low. On the other hand,

a large-breed dog with a cervical lesion and contrast medium injection in the cerebellomedullary cistern would have a higher risk. However, the risk of seizure can be minimized in large-breed dogs by limiting the total volume of iohexol injected to 8 mL and by performing the injection into the lumbar cistern.

a. SAS, version 8.2, SAS Institute Inc, Cary, NC.

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