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Comparative Neurotoxicity of Intrathecal and Epidural Lidocaine in Rats

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Background: **Although there is a considerable difference in the number of clinical reports of neurologic injury between spinal anesthesia and other regional techniques, there are no animal data concerning a difference in the local anesthetic neurotoxicity between intrathecal and epidural administration. In the current study, the functional and morphologic effects of lidocaine administered intrathecally and epidurally were compared in rats.**

Methods: **Male rats were implanted with an intrathecal or epidural catheter through L4–L5 vertebra in the caudal direction. In experiment 1, to determine relative anesthetic potency, 16 rats received repetitive injections of 2.5% lidocaine into intrathecal or epidural space in different volumes and were examined for tail flick test for 90 min. In experiment 2, to ascertain whether the relative potency obtained in experiment 1 would apply to other concentrations of lidocaine, additional rats received saline, 1%, 2.5%, or 5% lidocaine in a volume of 20 or 100 μl through the intrathecal or epidural catheter, respectively. In experiment 3, additional rats that received saline, 2.5% lidocaine, or 10% lidocaine in a volume of 20 or 100 μl through the intrathecal or epidural catheter, respectively, were examined for persistent functional impairment and morphologic damage.**

Results: **In experiment 1, the two techniques produced parallel dose–effect curves that significantly differed from each other. The potency ratio calculated was approximately 4.72 (3.65–6.07):1 for intrathecal:epidural lidocaine. In experiment 2, every lidocaine solution produced a similar increase in tail flick latency for the two techniques. In experiment 3, five of eight rats given 10% intrathecal lidocaine incurred functional impairment 4 days after injection, whereas no rats in the other groups did. Significantly more morphologic damage was observed in rats given 10% intrathecal lidocaine than in those given 10% epidural lidocaine.**

Conclusions: **Persistent functional impairment occurred only after intrathecal lidocaine. Histologic damage in the nerve roots and the spinal cord was less severe after epidural lidocaine than after intrathecal lidocaine. The current results substantiate the clinical impression that neurologic complications are less frequent after epidural anesthesia than after spinal anesthesia.**

INCREASING laboratory evidence suggests that local anesthetics are potentially neurotoxic and that neurologic impairment following regional anesthesia may result from a direct neurotoxic effect of local anesthetics.[1–3] Serious neurologic sequelae, including cauda equina syndrome, have been reported to occur after neuraxial blockade.[4–10] In addition, transient neurologic symptoms, such as pain and dysesthesia in the buttocks and lower extremities, following neuraxial blockade have gathered considerable attention.[11–16] Although the cause and significance of these transient symptoms are unknown and a relationship to permanent neurologic injuries remains highly speculative, their occurrence has increased our concern regarding regional anesthetic techniques using local anesthetics.

There is a considerable difference in the number of reported cases between spinal anesthesia and other regional techniques.[8,17] In most of the cases, the former technique has been used. Although this fact may let us speculate that other techniques, such as epidural anesthesia, are safer than spinal anesthesia and rarely associated with the injury, no data exist to compare the neurotoxicity of local anesthetics administered intrathecally and epidurally. Most *in vivo* experiments have focused on neurotoxic effects of local anesthetics administered intrathecally,[1–3,18–22] and little is known concerning those of epidural local anesthetics. The lack of comparative studies may be the result of a lack of proper animal models with an epidural catheter at the same level as an intrathecal catheter. In the current study, we implanted both an intrathecal and an epidural catheter through the L4–L5 intervertebral space in the caudal direction in rats and compared the functional and morphologic effects of lidocaine administered intrathecally and epidurally.

Materials and Methods

The protocol was approved by the Animal Research and Use Committee of Shimane Medical University (permission No. 01–40). Male Sprague rats weighing 329 ± 19 g (mean ± SD) were housed in groups of four in metal cages on a 12-h light–dark cycle. After catheterization, they were moved to a plastic cage within wood chips individually. Food and water were provided *ad libitum*. To reduce the influences of handling on behavioral reactions, all rats were trained in the test situation at least three times before experiments. The rats were randomly divided into two groups for intrathecal or epidural catheterization.

Surgical Procedure

After administration of sodium pentobarbital (Dainippon Pharmaceutical, Osaka, Japan) (30 mg/kg intraperitoneally) with 1.5% halothane anesthesia, a heat-con-

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nected catheter of stretched polyethylene tubing PE-10 (1.3 cm), PE-10 (10 cm), and PE-20 (6 cm) was introduced into the subarachnoid or epidural space using an aseptic technique. Catheters were passed through the L4–L5 intervertebral space and advanced 1.3 cm in the caudal direction. Before starting the experiments, rats were allowed 4 days to rest for recovery from the operation. Rats having any problem with tail movements or motor dysfunction in the hind limbs were not used in the ensuing experiments.

Measurement of Neurologic Function

To measure the response of the tail to noxious heat stimulus, a tail flick (TF) test was performed using TF equipment (model DS20; Ugo Basile, Comerio-Varese, Italy). A 100-W projector lamp was focused on a distal segment of the tail approximately 5 cm from the tip. The time at which rats withdrew the tail was defined as the TF latency. A cutoff time of 10 s was used to avoid damage to the tail.

To measure the response of the legs to noxious mechanical stimulus, a paw pressure (PP) test was applied to the dorsal surface of both hind paws using a device (type 7200; Ugo Basile, Comerio-Varese, Italy) capable of progressively increasing the pressure at a rate of 15 g/s. The pressure at which rats withdrew the paw from the device was defined as the PP threshold, and the mean value of both paws was used for analysis. A cutoff pressure of 400 g was used to prevent damage to the paws.

Motor function (MF) in the lower limbs was also assessed. The grading of the motor block was as follows: 0, none; 1, partially blocked; and 2, completely blocked. The normal baseline score was 0, and the score with bilateral complete block was 2 + 2 = 4. TF, PP, and MF tests were performed sequentially at the same time point with a 15-s interval.

Experimental Protocol

In experiment 1, to determine relative anesthetic potency for intrathecal and epidural lidocaine, 16 rats repetitively received 2.5% lidocaine intrathecally (n = 8) in 5, 8, 13, and 20 μl or epidurally (n = 8) in 25, 40, 64, and 100 μl. Ten microliters of saline was then injected to flush the catheter. The TF test was performed 10, 15, 20, 25, 30, 45, 60, and 90 min after the drug administration. The intervals between injections were at least 24 h.

In experiment 2, after the measurement of baseline TF latency, additional rats with an intrathecal or epidural catheter were randomly divided into four groups to intrathecally receive normal saline (IT-S, n = 6), 1% lidocaine (IT-L1, n = 6), 2.5% lidocaine (IT-L2.5, n = 6), or 5% lidocaine (IT-L5, n = 5), or to epidurally receive normal saline (EP-S, n = 6), 1% lidocaine (EP-L1, n = 7), 2.5% lidocaine (EP-L2.5, n = 6), or 5% lidocaine (EP-L5, n = 5). Each solution was given in a volume of 20 μl intrathecally and 100 μl epidurally followed by 10 μl saline to flush the catheter. Measurements of the TF test were repeated 10, 15, 20, 25, 30, 45, 60, and 90 min after the drug administration. At the end of the experiments, 2% lidocaine was injected intrathecally (10 μl) or epidurally (50 μl) followed by 10 μl normal saline to validate the function of the catheter 5 min after the administration. Rats that showed no increase in the TF latency were excluded from the data analysis.

In experiment 3, after the measurement of the baseline values, one of the following solutions was randomly administered by bolus into additional rats with either catheter: intrathecal normal saline (IT-S, n = 7), 2.5% lidocaine (IT-L2.5, n = 7), or 10% lidocaine (IT-L10, n = 8), or epidural normal saline (EP-S, n = 7), 2.5% lidocaine (EP-L2.5, n = 7), or 10% lidocaine (EP-L10, n = 8). In addition, 16 rats with an intrathecal or epidural catheter were randomly divided into two groups to intrathecally receive saline alone (n = 4) or saline mixed with 0.1 N hydrochloric acid (pH-adjusted saline) (n = 4), or to epidurally receive saline alone (n = 4) or pH-adjusted saline (n = 4). Saline and 0.1 N hydrochloric acid were combined to have a pH slightly lower than that of 10% lidocaine solution. Each solution was given in a volume of 20 μl intrathecally and 100 μl epidurally followed by 10 μl saline to flush the catheter. Measurements of the TF, PP, and MF tests were repeated 10, 20, 30, 60, 120, 180, and 240 min after drug administration and continued daily for 4 days.

Crystalline lidocaine hydrochloride (Sigma Chemical, Steinheim, Germany) was dissolved in sterile distilled water (Otsuka Pharmaceutical, Tokyo, Japan) immediately before injection. All solutions were administered manually by a single bolus injection using a microsyringe at a rate of approximately 10 μl/15 s. The osmolarity and pH of all the solutions were measured (Osmometer, OSA-22; Nikkiso, Tokyo, Japan; and pH meter, F-22, Horiba, Kyoto, Japan).

Tissue Preparation

After the last measurements in experiment 3, the rats were euthanized by injection of an overdose of pentobarbital and then perfused intracardially with a phosphate-buffered 2.0% paraformaldehyde–2.5% glutaraldehyde fixative. Methyl green solution was injected to confirm the location of the catheter after the perfusion. The spinal cord and nerve roots were dissected out and immersed in the same fixative for 4 h. Two specimens (10 mm rostral and caudal to the conus medullaris) from each rat were postfixed with cacodylate-buffered 1% osmium tetroxide, dehydrated in a series of graded alcohol solutions, and embedded in epoxy resin. From the embedded tissue, 1-μm transverse sections were obtained using the microtome (MT6000; RMC, Tucson, AZ) and stained with toluidine blue dyes. Neuropathologic examination was conducted using light microscopy by a pathologist who was masked to the group assignment

and the results of functional assessments. Sections obtained from 10 mm rostral to the conus (caudal spinal cord) were used for qualitative evaluation. Quantitative analysis of nerve injury was performed using the sections obtained from 10 mm caudal to the conus (cauda equina). Each fascicle present in the cross section was assigned an injury score of 0–3 (0 = normal, 1 = mild, 2 = moderate, and 3 = severe). The details of the nerve injury scoring system have been published previously.[2] The injury score for each cross section was then calculated as the average score of all the fascicles present in the cross section.

Statistical Analysis

Data are presented as mean ± SEM unless otherwise stated. TF latencies and PP thresholds were converted to the percentage of the maximal possible effect, calculated as (postdrug value − baseline value)/(cutoff value − baseline value) × 100%. The area under the time–effect curve (AUC) was calculated by accumulating the effect measured at the discrete time intervals using the trapezoidal integration method. The dose–effect relationship for anesthesia was determined by using AUC values, and the dose–effect curves for the two techniques were tested for parallelism, and the potency ratio calculated and tested for significance according to the method described by Tallarida and Murray.[23] The results of the TF and PP tests were analyzed by ANOVA with repeated measures followed by Scheffe and Dunnett tests; intergroup comparisons were made for each technique and for each solution. Differences of AUC between intrathecal and epidural administration of each solution were analyzed using the Student *t* test. The injury score for each technique or for each solution was compared using two-way ANOVA followed by the Scheffe test. MF was analyzed by the Kruskal–Wallis test, and the differences between intrathecal and epidural administration of each solution were analyzed by Mann–Whitney U test. The frequency (*i.e.*, the number of rats with lesions) in each group was analyzed by chi-square test. A *P* value less than 0.05 was considered to be statistically significant.

Results

In experiments 1, 2, and 3, a total of two, five, and eight rats, respectively, were excluded from the study because of catheter failure. The number of rats that completed each experiment was listed in Materials and Methods. The pH and osmolarity of solutions used are listed in table 1.

Experiment 1

Intrathecal and epidural administration of 2.5% lidocaine produced parallel dose–effect curves that significantly differed from each other (fig. 1). The potency ratio calculated was approximately 4.72 (95% CI, 3.65–6.07):1 for intrathecal:epidural lidocaine.

Table 1. Physical Characteristics of Solutions Studied

Solution	pH	mOsm/l
Normal saline	5.90 ± 0.19	291 ± 1
1% lidocaine	4.60 ± 0.33	72 ± 7
2.5% lidocaine	4.63 ± 0.13	162 ± 1
5% lidocaine	4.35 ± 0.20	319 ± 4
10% lidocaine	4.30 ± 0.16	624 ± 2
Normal saline with 0.1 N HCl	4.19 ± 0.06	289 ± 0

Values are presented as mean ± SD.
HCl = hydrochloric acid.

Experiment 2

Baseline TF latencies did not differ among groups. TF latency did not change in rats given IT-S or EP-S during the experiment (fig. 2). Every lidocaine solution given intrathecally or epidurally produced a significant increase in TF latency. TF latency in IT-L1 and EP-L1 was significantly higher than that in IT-S and EP-S, respectively, for 15 min after the injection. TF latency in IT-L2.5 and EP-L2.5 was significantly higher than that in IT-S and EP-S, respectively, for 20 min after the injection. Whereas TF latency in IT-L5 was significantly higher than that in IT-S for 30 min after the injection, epidural 5% lidocaine produced significantly higher TF latencies for 25 min after the injection than did epidural saline. There were no differences in AUC between intrathecal and epidural administrations of each solution.

Experiment 3

Baseline TF latencies and PP thresholds did not differ among groups. TF latency and PP threshold did not change in rats given saline through either catheter throughout the experiment. Neither IT-L2.5 nor EP-L2.5 was associated with a persistent increase in TF latency except for the first 20 min after the injection (fig. 3). TF latencies in EP-L10 returned to the baseline values after

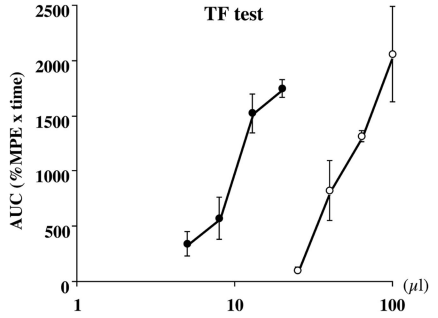

Fig. 1. Dose–effect curves after the administration of 2.5% lidocaine intrathecally and epidurally. The *x* axis shows the volume of 2.5% lidocaine, and the *y* axis shows the area under the curve (AUC). Data are presented as mean ± SEM. ● = intrathecal; ○ = epidural; %MPE = percent maximal possible effect; TF = tail flick.

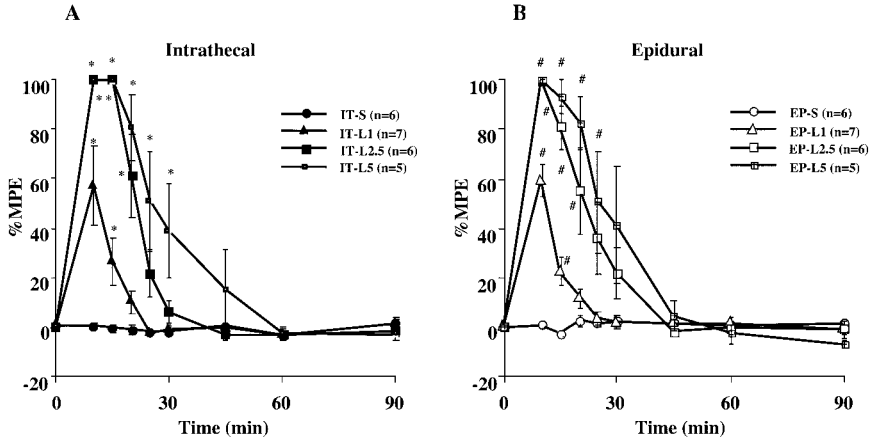

Fig. 2. Time-course effects on percent maximal possible effect (%MPE) in the tail flick test after the intrathecal administration of saline (IT-S), 1% lidocaine (IT-L1), 2.5% lidocaine (IT-L2.5), or 5% lidocaine (IT-L5) (*A*), or after the epidural administration of saline (EP-S), 1% lidocaine (EP-L1), 2.5% lidocaine (EP-L2.5), or 5% lidocaine (EP-L5) (*B*). Data are presented as mean ± SEM. **P* < 0.05 compared with IT-S. #*P* < 0.05 compared with EP-S.

60 min, whereas rats in the IT-L10 group showed a persistent increase in TF latency for 3 days. In addition, TF latencies in five of the eight rats in the IT-L10 group did not return to the baseline values, and two continued to show cutoff values until 4 days after injection. The difference in TF latency between IT-L10 and EP-L10 was significant from 120 min to 4 days.

Paw pressure threshold increased temporarily in rats given 2.5% and 10% lidocaine epidurally and intrathecally, but it showed no persistent increase after injection except for one rat in the IT-L10 group, which showed significant increases in PP threshold in the left hind limb 3 and 4 days after drug administration (fig. 4). The difference in PP threshold between IT-L10 and EP-L10 was significant after 20 and 30 min.

No rats given saline intrathecally or epidurally developed motor block during the experiment (table 2). Rats in the IT-L10 group showed significantly higher motor block scores than did those in the EP-L10 group after 20 and 30 min. However, the decrease in MF was observed only temporarily in any rats given lidocaine.

Sections obtained from the cauda equina of animals in the IT-L2.5 and EP-L2.5 groups showed only mild damage in the fascicles, and the average nerve injury scores did not differ from those in the IT-S and EP-S groups, respectively. Those obtained from rats in the IT-L10 group showed moderate-to-severe injury, and the nerve injury score was significantly higher than that for the IT-S group, whereas sections obtained from rats given the same solution epidurally did not show severe histologic damage and were not different from those observed in rats given saline (fig. 5). Representative sections from animals in each group are shown in figure 6. Histologic changes in nerve roots were characterized by edema and axonal degeneration, including appearance of myelin ovoid, and swelling, atrophy, and loss of axons with macrophage infiltration.

Histologic examination of the spinal cord showed axonal degeneration in the white matter and vacuolar degeneration of neurocytes in the gray matter, in addition to the infiltration of macrophages in rats given 10% lidocaine (figs. 7 and 8). Although the former changes were observed in the EP-L10 and IT-L10 groups, the latter changes in the gray matter were present only in rats in the IT-L10 group (table 3).

There were no significant differences between saline and pH-adjusted saline in TF, PP, and MF tests in intrathecal and epidural administration. Histologic changes observed in rats given pH-adjusted saline were minimal and did not differ from those in rats given saline alone with an intrathecal (injury score, 0.037 ± 0.019 and 0.042 ± 0.017 after saline alone and pH-adjusted saline, respectively) or epidural catheter (injury score, 0.040 ± 0.028 and 0.042 ± 0.021 after saline alone and pH-

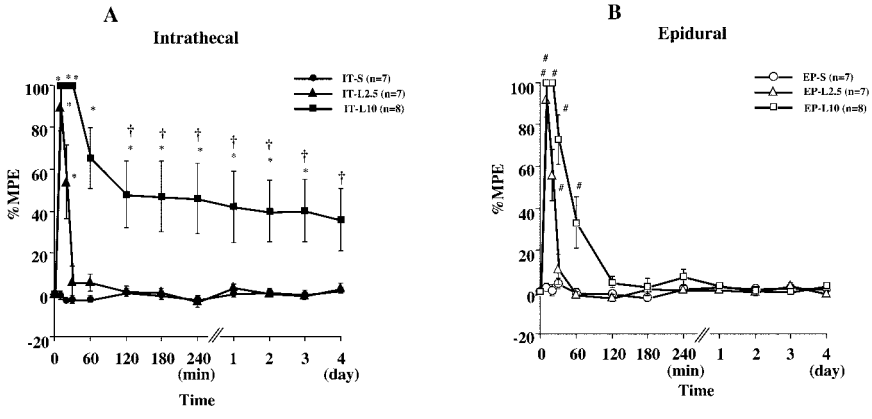

Fig. 3. Time-course effects on percent maximal possible effect (%MPE) in the tail flick test after the intrathecal administration of saline (IT-S), 2.5% lidocaine (IT-L2.5), or 10% lidocaine (IT-L10) (*A*), or after the epidural administration of saline (EP-S), 2.5% lidocaine (EP-L2.5), or 10% lidocaine (EP-L10) (*B*). Data are presented as mean ± SEM. **P* < 0.05 compared with IT-S. #*P* < 0.05 compared with EP-S. †*P* < 0.05 compared with EP-L10.

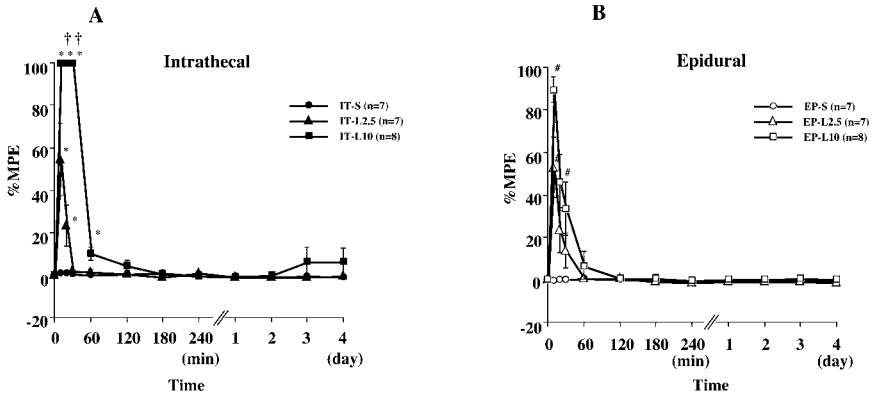

Fig. 4. Time-course effects on percent maximal possible effect (%MPE) in the paw pressure test after the intrathecal administration of saline (IT-S), 2.5% lidocaine (IT-L2.5), or 10% lidocaine (IT-L10) (*A*), or after the epidural administration of saline (EP-S), 2.5% lidocaine (EP-L2.5), or 10% lidocaine (EP-L10) (*B*). Data are presented as mean ± SEM. **P* < 0.05 compared with IT-S. #*P* < 0.05 compared with EP-S. †*P* < 0.05 compared with EP-L10.

adjusted saline, respectively). There were no apparent histologic changes in the spinal cords in both groups.

Discussion

Three experiments were performed. In the first, the dose–effect relationship for intrathecal and epidural lidocaine in rats (*i.e.*, the relationship between volume of 2.5% lidocaine and function of the tail) was determined, and the potency ratio for the two techniques was calculated. The second experiment was performed to ascertain whether the relative potency obtained using the fixed concentration of lidocaine would apply to other concentrations of lidocaine. We administered three concentrations of lidocaine into intrathecal and epidural spaces in volumes of 20 μl and 100 μl, respectively, with the ratio based on the result of the first experiment. Because both techniques showed similar analgesic effects with other concentrations of lidocaine, experiment 3 was performed to compare the neurotoxic effects of epidural and spinal lidocaine in volumes of 20 μl and 100 μl, respectively.

To the best of our knowledge, this is the first study to examine the neurotoxicity of local anesthetics administered in the epidural space. Moreover, this is the first study to compare the neurotoxic effects between epidural and intrathecal local anesthetics, and the anesthetic effects of the two techniques have seldom been compared. Animal models that permit comparison of the effects of agents administered intrathecally and epidurally are scarce. An appropriate model should have agents delivered at a similar level with both techniques. In the current study, we inserted an intrathecal or epidural catheter through the L4–L5 intervertebral space to advance 1.3 cm caudally. Therefore, it is likely that although the intrathecal catheter was among the nerve roots of the cauda equina and the epidural one outside the dura mater, the tip of the two catheters was placed at the same level.

Anesthetic potencies have usually been determined by using a peak value or a value at a certain time after drug administration. However, because intrathecal and epidural anesthesia differ in mechanism and, thus, onset and peak times, duration, and so forth, a single value at one point may not reflect the net effects of agents administered. Therefore, we calculated the AUC to compare the anesthetic effects of the two. The resulting potency ratio calculated in experiment 1 and confirmed in experiment 2 was approximately 5:1 for intrathecal: epidural lidocaine. The ratio was the reverse of the ratio of volumes that could produce the same anesthetic effects with the two techniques. Although equivalent relative potencies would not necessarily be expected in different models, our findings agree closely with our clinical experience, in which intrathecal and epidural local anesthetics are administered by a single bolus in volumes in a similar ratio.

Table 2. Motor Function after Drug Injection

Group	n	0 (min)	10	20	30	60	120	180	240	1 (day)	2	3	4
IT-S	7	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
IT-L2.5	7	0 (0, 0)	2 (1, 4)	3 (1, 3)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
IT-L10	8	0 (0, 0)	4 (4, 4)	4 (4, 4)*	4 (4, 4)*	0 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
EP-S	7	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
EP-L2.5	7	0 (0, 0)	2 (1, 3)	1 (0, 2)	0 (0, 2)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
EP-L10	8	0 (0, 0)	4 (2, 4)	3 (1, 4)	2 (0, 2)	0 (0, 2)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Values are median (10th, 90th percentiles).

* $P < 0.05$ compared with EP-L10.

EP-S = epidural normal saline; EP-L2.5 = epidural 2.5% lidocaine; EP-L10 = epidural 10% lidocaine; IT-S = intrathecal normal saline; IT-L2.5 = intrathecal 2.5% lidocaine; IT-L10 = intrathecal 10% lidocaine.

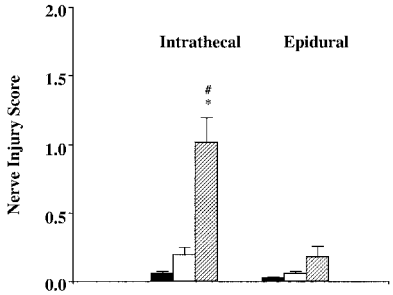

Fig. 5. Nerve injury score for sections obtained 10 mm caudal to the conus 4 days after administration of saline (■), 2.5% lidocaine (□), or 10% lidocaine (▨), intrathecally or epidurally. Each fascicle was assigned an injury score of 0–3 (0 = normal, 1 = mild, 2 = moderate, 3 = severe). The injury score for each cross section was calculated as the average score of all fascicles in the section. Data are presented as mean ± SEM. *$P < 0.05$ compared with intrathecally administered normal saline and 2.5% lidocaine. #$P < 0.05$ compared with epidurally administered 10% lidocaine.

The current results show that intrathecal lidocaine induces functional impairment and histologic damage in rats to a more severe degree than epidural lidocaine. The reason for the difference between epidural and intrathecal lidocaine is highly speculative but may be related to different pharmacokinetics between the two.[24] Epidurally administered local anesthetics exert their effects by more complicated mechanisms than those intrathecally administered. Possible sites of action of local anesthetic administered epidurally include the nerve trunks

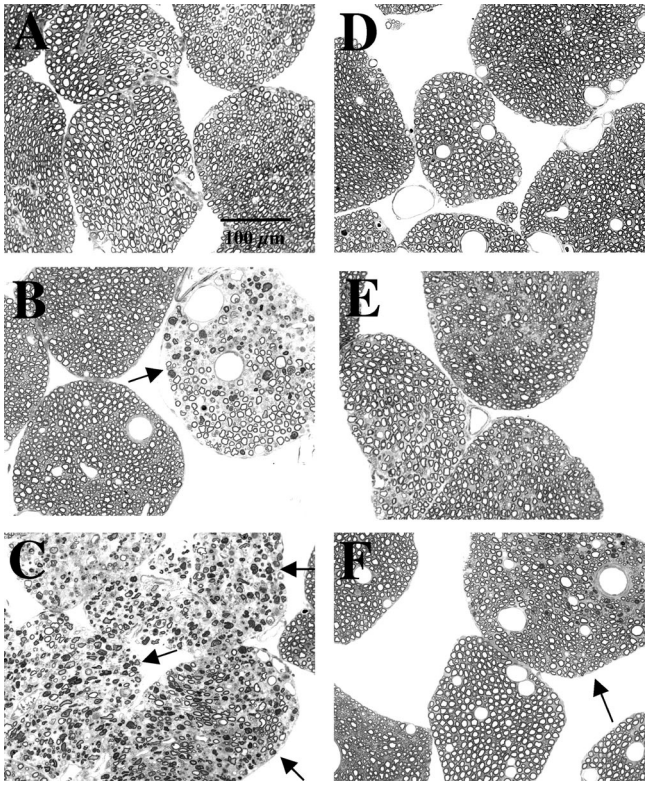

Fig. 6. Transverse sections obtained from 10 mm caudal to the conus 4 days after the intrathecal administration of saline (*A*), 2.5% lidocaine (*B*), or 10% lidocaine (*C*), or after the epidural administration of saline (*D*), 2.5% lidocaine (*E*), or 10% lidocaine (*F*). *Arrows* indicate damaged fascicles in the cauda equina. Histologic changes in the cauda equina were characterized by edema and axonal degeneration, including appearance of myelin ovoid, and swelling, atrophy, and loss of axons with macrophage infiltration.

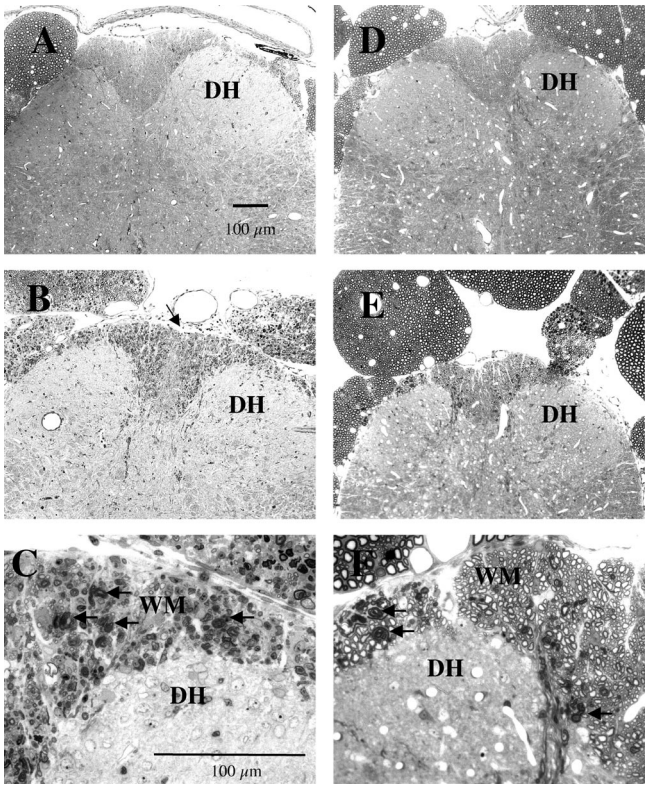

Fig. 7. Transverse sections obtained from 10 mm rostral to the conus 4 days after the intrathecal administration of saline (*A*) or 10% lidocaine (*B*), or after the epidural administration of saline (*D*) or 10% lidocaine (*E*). Normal spinal cords were observed in *A* and *D*. The *arrows* in *B* and *E* show damaged white matter in the spinal cord. Parts *C* and *F* show higher magnification of *B* and *E*, respectively. The arrows of *C* and *F* show axonal degeneration. DH = dorsal horn; WM = white matter.

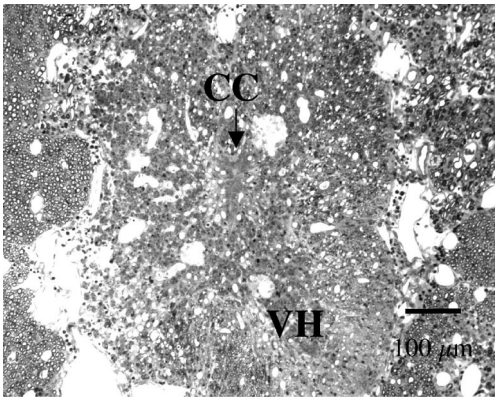

Fig. 8. A transverse section obtained from 10 mm rostral to the conus 4 days after the intrathecal administration of 10% lidocaine. Gray matter and white matter in the spinal cord was damaged. Histologic changes in the gray matter are characterized by vacuolar degeneration of neurocytes and macrophage infiltration. CC = central canal; VH = ventral horn.

Table 3. Frequency (Number of Rats in Each Group) of Lesions in the Caudal Spinal Cords

		Caudal Spinal Cord				
		White Matter			Gray Matter	
Group	n	Posterior	Lateral	Anterior	Dorsal	Ventral
IT-S	7	0	0	0	0	0
IT-L2.5	7	1	0	0	0	0
IT-L10	8	6*	3	3	2	2
EP-S	7	0	0	0	0	0
EP-L2.5	7	0	0	0	0	0
EP-L10	8	1	0	0	0	0

* $P < 0.05$ compared with EP-L10.

EP-S = epidural normal saline; EP-L2.5 = epidural 2.5% lidocaine; EP-L10 = epidural 10% lidocaine; IT-S = intrathecal normal saline; IT-L2.5 = intrathecal 2.5% lidocaine; IT-L10 = intrathecal 10% lidocaine.

in the paravertebral space, spinal nerves intradurally, and the spinal cord. Epidural local anesthetic spreads to the dural sleeves, where the dura matter is thin with arachnoid proliferations and villi.[25] Subsequently, the drug diffuses into the cerebrospinal fluid[26] and causes nerve blocks on the nerve roots and on the spinal cord. Thus, local anesthetic in the cerebrospinal fluid should play a limited role in producing blocking effects after epidural administration. It was shown that intrathecal concentration of local anesthetic after epidural administration is lower than that after intrathecal administration.[27]

One possible criticism against the protocol of the current study may be that the technique used for intrathecal and epidural administration does not necessarily reflect routine clinical use of the two techniques. Most important, both injections are sometimes performed repeatedly. In addition, although both techniques were equal in analgesic effects, as shown in experiments 1 and 2, it is possible that the intensity of the nerve block produced by the two is different, because intrathecal 10% lidocaine produced more profound motor block than epidural lidocaine for the first 30 min after the injection in experiment 3. Clinically, however, the two anesthetic techniques hardly produce similar blocking effects, even when local anesthetic is administered more than five times into the epidural space than into the intrathecal space. If we encountered a complete motor blocking effect after single epidural anesthesia, we would suspect that there was a dural puncture.

The lidocaine solutions used in the current experiments, as in previous studies,[2,3] were prepared by dissolving crystalline lidocaine hydrochloride in sterile distilled water and had a pH that was lower than clinically available lidocaine. It is unlikely that the functional impairment and morphologic damage after intrathecal injection of 10% lidocaine are not relevant to clinical injury and that the acidity of the solutions mainly contributed to the neurotoxicity. All the lidocaine solutions prepared had a similar pH, and only the highest concentration of lidocaine induced injury. In addition, animals given saline with hydrochloric acid that had a lower pH than lidocaine solutions were almost identical with those given saline alone for the functional and morphologic findings.

Because local anesthetic solutions clinically administered rarely induce neurologic injury, the observation of neurotoxic effects would require a larger dose of agents. For example, to produce injury, Drasner *et al.*[18] used a rat model, in which local anesthetics were continuously infused. In the current study, in contrast, we increased the concentration of local anesthetic. As a result, the concentration of lidocaine that induced neurologic damage in the current study exceeds that used clinically by far. Thus, the functional impairment and morphologic damage observed may not be clinically relevant. However, that rats given 10% epidural lidocaine incurred only minimal morphologic damage without functional impairment indicates that the epidural technique is associated with neurotoxicity far less than the intrathecal technique.

Despite our results, the inadvertent intrathecal administration of intended epidural local anesthetic can occur in a clinical situation.[6] Because much larger doses of local anesthetic are usually administered for epidural anesthesia than for spinal anesthesia, as in the current study, neural tissue in the subarachnoid space could be exposed to a toxic concentration of anesthetic.

In conclusion, when intrathecal and epidural lidocaine were administered to produce similar anesthetic effects, persistent functional impairment occurred only after intrathecal injection of lidocaine in rats. Histologic damage in the nerve roots and the spinal cord was less severe after injection with epidural lidocaine than with intrathecal lidocaine. The current results substantiate our clinical impression that neurologic complications are less frequent after epidural anesthesia than after spinal anesthesia.

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