Lidocaine Concentration in Cerebrospinal Fluid after Epidural Administration

A Comparison between Epidural and Combined Spinal–Epidural Anesthesia

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Background: In this study, lidocaine concentrations in cerebrospinal fluid (CSF) at different interspaces were measured with or without preceding spinal anesthesia, 10 min after epidural injection of lidocaine, to investigate the effects of preceding meningeal puncture on CSF concentrations of epidurally administered local anesthetic.

Methods: Sixty patients scheduled to receive combined spinal–epidural anesthesia were randomly allocated to receive either spinal anesthesia first (group CSEA) or epidural lidocaine first (group Epi). Each group was divided into three subgroups in which the site of epidural cannulation and spinal tap were separated by one, three, or five interspaces (sets I, II, and III, respectively). CSF was collected from the L4–L5 interspace 10 min after 10 ml lidocaine, 1%, was administered epidurally. In group Epi, CSF was collected after epidural administration of lidocaine and before spinal anesthesia. In group CSEA, spinal anesthesia was performed at the L3–L4 interspace after epidural cannulation and epidural lidocaine was administered postoperatively, after which CSF was sampled.

Results: Lidocaine concentrations in CSF were significantly higher with increasing proximity of epidural injection site to CSF collection site in both groups. There were no significant differences in CSF lidocaine concentrations between group CSEA and group Epi in set I, although lidocaine concentrations were significantly higher in group CSEA set II and III patients.

Conclusion: Lidocaine concentration in CSF was similar with or without preceding meningeal puncture beneath the epidural administration site.

COMBINED spinal–epidural anesthesia (CSEA) is now a popular technique in obstetric and gynecologic surgery, including cesarean delivery and surgery of the lower extremities.[1–3] Advantages include rapid onset, profound neuraxial block, and the ability to titrate or prolong blockade and lower total drug dosage.[4] However, there is concern about epidurally administered drugs spreading into the subarachnoid space through the meningeal hole made by the spinal needle.[5,6] Although we have administered local anesthetics and/or opioids (morphine or fentanyl) for surgical anesthesia and postoperative pain relief, we were unsure of the exact extent to which epidurally administered local anesthetics would pass through the meningeal hole; the actual concentrations of anesthetics in the cerebrospinal fluid (CSF) in the clinical setting of CSEA were also unknown. The current study was designed to estimate the extent to which epidural lidocaine spreads into the subarachnoid space and to clarify the effects of varying the distance between the meningeal puncture and epidural injection sites.

Materials and Methods

Subjects

This study was done solely at Chigasaki Municipal Hospital (Chigasaki, Kanagawa, Japan) after approval by the ethics committee of the institution, and all subjects provided written informed consent before enrollment. Subjects comprised 61 patients (American Society of Anesthesiologists physical status I or II) scheduled to undergo elective gynecologic surgery (transabdominal hysterectomy, transvaginal hysterectomy, oophorectomy). Before anesthesia, all patients underwent anterior–posterior view of abdominal radiography to determine the integrity of the vertebrae and to confirm that the iliac crest could be used as a landmark for identifying the vertebral interspace. Patients with vertebral deformity (scoliosis and/or kyphosis), compression fractures of vertebrae that made identification of the vertebral interspace on abdominal radiography difficult, or a history of spinal surgery were excluded from the study.

Experimental Design and Anesthetic Procedure

Before the induction of anesthesia, patients who were scheduled to receive CSEA were randomly allocated to receive either spinal anesthesia first (group CSEA) or epidural administration of lidocaine first (group Epi), each group being further divided into three subgroups depending on whether the site of epidural cannulation and spinal tap were separated by one, three, or five interspaces (sets I, II, and III, respectively). The opening of sealed envelopes method was used for random allocation. For preliminary analysis, 10 patients were initially randomly allocated to each subgroup, another patient being enrolled to replace a patient who dropped out of

the study. All patients were given 0.5 mg atropine sulfate, 50 mg hydroxyzine, and 20 mg famotidine intramuscularly 30 min before transfer to the operating room, and 500 ml lactated Ringer's solution before anesthetic induction.

Patients were monitored using electrocardiography, a noninvasive blood pressure cuff every 5 min, and pulse oximetry during anesthesia. With the patient in the right lateral decubitus position, the epidural space was identified at the L3–L4 interspace (group Epi-I, group CSEA-I), the L1–L2 interspace (group Epi-II, group CSEA-II), or the T11–T12 interspace (group Epi-III, group CSEA-III) by the loss of resistance technique using a 17-gauge Tuohy needle (Mini Kit; Abott, Sligo, Ireland). Air was used for the loss-of-resistance technique, and no liquid was injected into the epidural space before insertion of the epidural catheter. After the epidural space was identified, the needle tip was positioned cephalad and a radiopaque epidural catheter (Flextip Plus Epidural Catheter; Arrow, Reading, PA) was introduced 5 cm from the needle tip.

In group Epi, 10 ml lidocaine, 1%, was injected *via* the catheter just after epidural catheterization. Ten minutes after lidocaine injection, spinal tap was performed at the L4–L5 interspace using a 25-gauge spinal needle with Quincke tip (Top Spinal Needle®; Top, Tokyo, Japan). The bevel of the spinal needle was inserted parallel to the long axis of the spine. Next, 0.5 ml CSF was aspirated and discarded to prevent picking up the lidocaine in epidural space, and then another 0.5 ml CSF was aspirated for measurement of lidocaine concentration, after which 2.0–2.4 ml hyperbaric tetracaine, 0.5%, was injected.

In group CSEA, nothing was injected *via* the catheter before spinal anesthesia. Just after epidural catheterization, the patient received a subarachnoid injection of 0.5% hyperbaric tetracaine (2.0–2.4 ml) at the L3–L4 interspace using a 25-gauge spinal needle with Quincke tip.

After performing spinal anesthesia, patients were immediately placed in the supine position, and the spread of sensory block was tested by the pinprick method. After sensory block reached the T4 level, surgery was commenced. Patients who required sedation received intravenous midazolam. Intraoperatively, oxygen was administered *via* facemask. If a patient in group CSEA reported intraoperative pain, the patient was excluded from the study and 3 ml lidocaine, 2%, was administered *via* the epidural catheter and repeated as necessary.

After the completion of surgery, patients in group CSEA were turned to a right lateral decubitus position and 10 ml lidocaine, 1%, was injected through the epidural catheter. A spinal tap was performed at the L4–L5 interspace, and 0.5 ml CSF was aspirated 10 min after lidocaine administration for measurement of CSF lidocaine concentration. Patients in group CSEA were then observed for more than 30 min in the operating room and returned to the ward. A detailed timeline of the study is shown in figure 1. The epidural catheter was used for postsurgical pain relief with continuous infusion of 0.25% bupivacaine.

Data Collection

The time between initiation of spinal anesthesia and administration of epidural lidocaine in group CSEA was recorded. The distance between the epidural catheter tip and interspace used for catheter insertion was determined by both anesthesiologist and surgeon on anterior–posterior view of abdominal radiography at the end of surgery.

Collected CSF samples were stored at −80°C until biochemical analysis. Lidocaine concentration in CSF
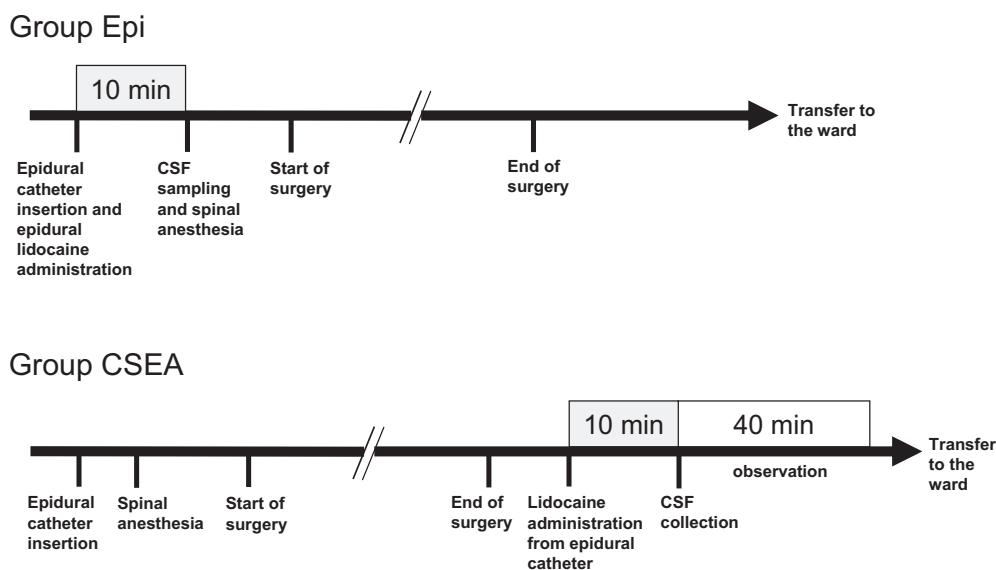

Fig. 1. Demographic flowchart indicating the time course of the study. CSEA = combined spinal–epidural anesthesia; CSF = cerebrospinal fluid; Epi = epidural anesthesia as control.

Table 1. Patient Characteristics

	CSEA-I	CSEA-II	CSEA-III	Epi-I	Epi-II	Epi-III	P Value*
Age, yr	49.4 ± 12.6	48.0 ± 11.1	44.3 ± 7.0	45.4 ± 3.2	41.9 ± 10.8	46.7 ± 5.7	0.751
Height, cm	155.3 ± 3.5	154.1 ± 6.6	155.9 ± 3.8	154.7 ± 5.4	154.7 ± 6.0	157.2 ± 7.3	0.973
Weight, kg	51.6 ± 8.9	53.3 ± 8.2	50.6 ± 5.7	57.8 ± 7.3	58.2 ± 7.3	55.3 ± 5.4	0.132

Data are shown as mean ± SD.

* With one-way analysis of variance.

CSEA = combined spinal–epidural anesthesia; Epi = epidural anesthesia as control.

was analyzed by fluorescence polarization immunoassay, as described in detail elsewhere,[7] by an analytical company (Mitsubishi Chemical Medicine, Tokyo, Japan). The lower limit of detection is 0.1 μg/ml, and lidocaine concentrations less than 0.1 μg/ml were considered as zero.

Statistical Analysis

A formal power analysis could not be performed because of lack of data with a similar setup and procedure. The proposed sample size of 60 patients was mainly determined for practical reasons and to enable completion of the trial within a reasonable time frame. It also allowed exploration of the three subgroups of different sampling sites in the two anesthetic method groups.

Data were analyzed using SPSS for Windows version 12.0 (SPSS, Chicago, IL), and the results are presented as mean ± SD for data showing a normal distribution and as median (range) for data not showing a normal distribution. Demographic variables were analyzed using one-way analysis of variance. As the primary analysis, pairwise comparisons of lidocaine concentrations between groups Epi and CSEA for each of sets I, II, and III were analyzed using the Mann–Whitney U test. Comparisons of data within groups Epi and CSEA were performed using the Kruskal–Wallis test. All P values were two-tailed, and values of $P < 0.05$ for one-way analysis of variance, the Mann–Whitney U test, the Kruskal–Wallis test, and other tests were considered as statistically significant. For comparison of each set in groups Epi and CSEA, the Bonferroni correction was used for analyzing statistical significance ($P < 0.05/3 = 0.0167$).

Results

Of the 61 patients enrolled in this study, one patient in group CSEA-I was excluded after additional epidural anesthesia was required because of inadequate spinal anesthesia. Finally, 60 patients of similar age, height, weight, and catheter tip position, as determined by abdominal radiographic examination (table 1 and 2), were enrolled and allocated to group CSEA and group Epi (n = 30 each). No significant differences in durations from spinal tap to epidural lidocaine injection were identified among the three subgroups of group CSEA (table 2). No patient had evidence of accidental meningeal puncture with the epidural needle, or subarachnoid placement of epidural catheter with complications related to the intrathecal injection of 10 ml lidocaine (such as accidental high-level spinal anesthesia or total spinal anesthesia), and no major anesthetic complications were encountered. One patient in group CSEA and one in group Epi experienced post–dural puncture headache.

Lidocaine was detected in the CSF of all patients in group CSEA, although lidocaine concentrations in CSF samples of one patient in Epi-II and two patients in Epi-III were less than 0.1 μg/ml, these being considered as zero. There were significant outliers in CSEA-I, Epi-II, and Epi-III (one patient from CSEA-I and Epi-II and two patients from Epi-III). Nonparametric statistics were used in the analyses of CSF lidocaine concentration because data distribution did not show equal distribution ($P = 0.001$ with the Bartlett test). In group CSEA, the lidocaine concentration in CSF at L3–L4 (CSEA-I) was significantly higher than that at T11–T12 (CSEA-III) ($P < 0.001$, Mann–Whitney U test multiple comparison with Bonferroni correction), although no significant differ-

Table 2. Interval from Spinal Tap to Epidural Lidocaine Administration and Catheter Tip Position

	CSEA-I	CSEA-II	CSEA-III	Epi-I	Epi-II	Epi-III	P Value*
Interval from spinal tap to epidural lidocaine administration, min	91.5 ± 27.5	69.0 ± 16.4	74.5 ± 18.3				0.106
Catheter tip position, cm cephalad from insertion site in anterior–posterior view of abdominal radiography	1.4 ± 1.3	1.8 ± 1.6	1.4 ± 1.6	2.0 ± 0.9	2.1 ± 1.9	2.5 ± 2.2	0.651

Data are shown as mean ± SD.

* With one-way analysis of variance.

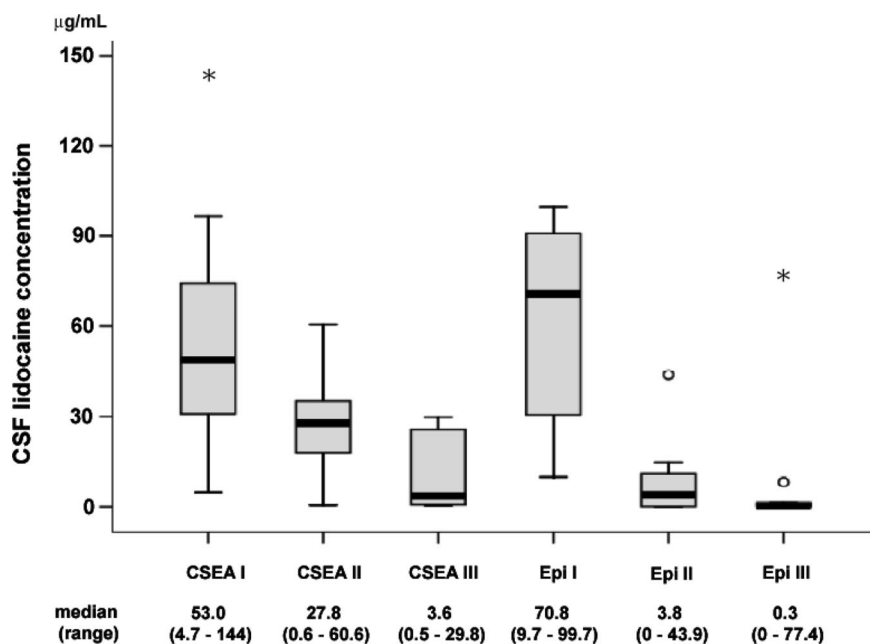CSEA = combined spinal–epidural anesthesia; Epi = epidural anesthesia as control.

Fig. 2. Lidocaine concentration in cerebrospinal fluid (CSF) at different interspaces with or without proceeding spinal anesthesia, 10 min after epidural injection of lidocaine. *Boxes* show interquartile range (IQR), *middle thick lines* show medians, and *whiskers* show the range of values falling within 1.5 IQR of the box. Values plotted with ° are greater than 1.5 IQR outside the box, and values plotted with * (extreme values) are greater than 3 IQR outside the box. CSEA = combined spinal–epidural anesthesia; Epi = epidural anesthesia as control.

ences were noted between Epi-I and Epi-II ($P = 0.151$) or between Epi-II and Epi-III ($P = 0.037$). Conversely, significant differences were identified between CSEA-I and CSEA-II ($P < 0.001$) and between CSEA-I and CSEA-III ($P < 0.001$). As for differences between groups CSEA and Epi, surprisingly, no differences were seen at L3–L4 ($P = 0.545$), although CSF lidocaine concentrations at L1–L2 and those at T11–T12 were significantly higher in group CSEA than in group Epi ($P = 0.006$ for L1–L2 and $P = 0.025$ for T11–T12, respectively; fig. 2). Moreover, the ratio of the amount of lidocaine in the CSF at each level in group CSEA divided by the amount in group Epi clearly showed a linear inverse relation ($R^2 = 0.991$; fig. 3).
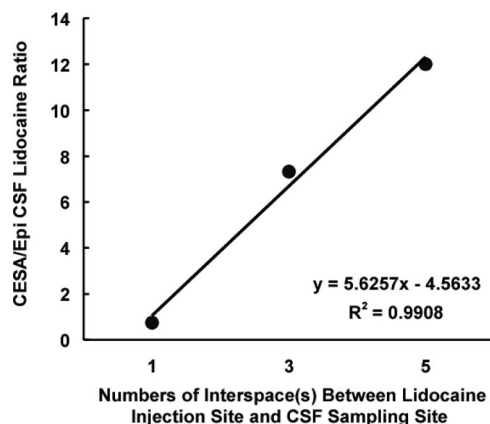

Fig. 3. Plot of the ratio of the amount of lidocaine in the cerebrospinal fluid (CSF) at each level in group CSEA divided by the amount in group Epi. There was a robust linear inverse relationship between the two groups. CSEA = combined spinal–epidural anesthesia; Epi = epidural anesthesia as control.

Discussion

This study investigated lidocaine concentrations in the CSF at the L4–L5 level when lidocaine was administered through an epidural catheter at different interspace distances from the CSF collection site, evaluating the influence of a prior meningeal hole in a clinical setting. To the best of our knowledge, this is the first study to compare concentrations of epidurally administered local anesthetics in CSF with or without the presence of a meningeal hole in clinical settings, although several studies have examined similar issues using *in vitro* settings or animal studies.[8–10] The two major findings of this study were that (1) lidocaine concentration in CSF decreased consistently with increasing distance from the site of CSF sampling, regardless of the presence or absence of a preceding meningeal hole; and (2) lidocaine concentrations between group CSEA and group Epi were almost similar at a distance of one interspace from the administration site, even though there were significant augmentations of lidocaine concentration in group CSEA compared with group Epi with increasing distance from the site of the meningeal puncture.

The most interesting finding, however, was that contrary to our expectations: There were no differences in lidocaine concentrations in the CSF with or without the meningeal hole, when the CSF collection site was at a distance of only one interspace from the administration site (set I), which is the case with needle-through-needle CSEA techniques, although the lidocaine concentration in CSF was significantly lower with a meningeal hole made by a 25-gauge spinal needle when the administration site was at a distance of more than three interspaces from the CSF collection site (sets II and III).

Several possibilities may explain the lack of a difference in lidocaine concentration in CSF in the presence or absence of a meningeal hole when the CSF collection site was close to the site of epidural lidocaine administration. Of most concern is the technical problem, in which the dura mater could be scratched and damaged by the epidural Tuohy needle and epidural lidocaine could easily penetrate into the intrathecal space. However, CSF concentrations collected at the same site in group Epi (without the meningeal hole) increased to around 60 μg/ml at 10 min after epidural administration of 100 mg lidocaine in this study, which seemed compatible with previous human clinical studies in which concentrations in CSF collected from the same interspace reached 100–250 μg/ml at 15–20 min after injection of 280–400 mg lidocaine into the lumbar epidural space.[11,12]

Another concern is contamination. When the collection site for CSF is so close to the site of epidural lidocaine administration, lidocaine in the epidural space might have been picked up through the spinal needle lumen when meningeal puncture was performed with the needle. However, when we collected CSF samples, we discarded initial CSF flow to prevent contamination. Furthermore, the data obtained in this study indicated that there are unlikely to be major technical problems in this study, even though we could not exclude this possibility completely.

One possibility accounting for the lack of difference in lidocaine concentration in CSF in set I is related to lidocaine permeability of the meningis. Lidocaine is one of the common local anesthetics in clinical use, with intermediate hydrophobic characteristics among local anesthetics.[8,13] In a previous study using monkey spinal meninges in an *in vitro* setting, lidocaine readily penetrated through meningeal tissue without a meningeal hole compared with morphine, which is considered to be a hydrophilic drug, and lidocaine transfer efficiency through meningeal tissue was not affected by the presence or absence of a hole, if the hole was adequately small.[8] The difference between this study and previous observations were the circumstances under which the drug was administered. In the living body, drug clearance that administered into the epidural space occurs primarily *via* uptake into the rather robust vascular supply in the dura mater.[14-16] Such drug elimination was theoretically absent in *in vitro* experimental settings, accounting for the differences in pharmacokinetics of lidocaine at local sites between these situations. In addition, with such a rapid penetration of lidocaine, equilibrium of the lidocaine concentration in CSF close enough to the administration site would be attained within a few minutes, even in the absence of a meningeal hole.

In both group CSEA and group Epi, lidocaine concentration in CSF was significantly lower with or without the meningeal hole, if the epidural lidocaine injection site was far enough from the CSF collection site. This finding can be explained by the property of epidurally administered local anesthetics to remain localized around the injection site, such that intrathecal local anesthetics might not affect the spinal nervous system above it, if drug dose is appropriate. However, lidocaine concentrations in CSF in group CSEA were significantly higher when lidocaine was administered at a distance of three to five interspaces away, compared with concentrations in group Epi. Moreover, we found that the ratio of the amount of lidocaine in the CSF at each level in group CSEA divided by the amount in group Epi showed a robust inverse linear relation (fig. 3).

These results suggests that a small amount of drug does migrate through the hole, but when the epidural local anesthetic is injected adjacent to the sampling site/meningeal puncture site, the amount that crosses through the hole into the CSF is trivial compared with that which crosses through the meninges. In contrast, when the lidocaine is injected into the epidural space distant from the sampling site, the concentration of lidocaine in CSF at the sampling site that results from diffusion across the meninges at the distant site is small and the contribution from the small amount that crosses through the hole is relatively greater. In this study, we did not analyze the speed of lidocaine penetration through meningeal tissues; we could not obtain time-course data for lidocaine concentration in CSF for ethical reasons, this being an obvious limitation of the current study. Also, because we did not radiologically examine the distribution of epidurally administered drugs using radiopaque dye, the spread of drugs administered through the epidural catheter could not be exactly determined. However, our results indicate that 10 ml lidocaine injected a distance of up to five interspaces from a meningeal hole can reach the hole and affect intrathecal lidocaine concentration by influx of the drug into the CSF through the hole.

Effects of a meningeal hole preceding epidural anesthesia are not yet completely understood. Epidural administration of local anesthetic after spinal anesthesia might affect the roots and intrathecal parts of peripheral nerves directly, and could affect the duration and spread of analgesia. In a healthy volunteer study, 10 ml epidurally injected lidocaine, 1.5%, administered immediately after spinal anesthesia with 50 mg lidocaine prolonged anesthetic duration but did not increase the area of the topped-up analgesia region.[17] Although the results of our study are apparently contradictory to those of this previous study, it is likely that epidurally administered lidocaine rapidly entered into the subarachnoid space, the increased amount of intrathecal lidocaine acting to prolong anesthetic duration. Also, Suzuki *et al.*[6] reported that dural puncture with a 26-gauge Whitacre spinal needle immediately before epidural injection of local anesthetics resulted in caudal spread of analgesia, without extensive cephalad effect of analgesia. They con-

cluded that only a small amount of local anesthetic spread into the subarachnoid space through the meningeal hole made by a 26-gauge Whitacre needle, which was consistent with our results. However, from a clinical standpoint, the existence of significant outliers in both groups reminds one about individual variations that the clinician must be cognizant of and vigilant for when using CSEA techniques.

In conclusion, we examined the extent to which epidural lidocaine spreads into the subarachnoid space and the effects of varying the distance between the meningeal puncture and epidural injection sites. Our results suggest that epidurally administered local anesthetics may spread into the subarachnoid space through meningeal tissue rather than directly through a preceding meningeal hole, thereafter remaining localized around the injection site. These results are consistent with some previous studies that have concluded that CSEA is basically safe and that dural holes have no influence on duration or anesthetic height after spinal anesthesia in patients undergoing cesarean delivery.[1,3,18,19] However, attention should be given to the adverse effects of drugs administered epidurally when CSEA is performed, particularly if spinal tap will be performed with a relatively large size spinal needle or in case of an accidental meningeal puncture made by a Tuohy needle.

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