Cerebrospinal norepinephrine concentrations and the duration of epidural analgesia

Fumio Goto MD PhD, Nao Fujita MD PhD,
Tatsushi Fujita MD PhD

This study was performed to determine whether the addition of norepinephrine to local anaesthetics prolongs epidural analgesia in man. In addition, cerebrospinal fluid norepinephrine (NE) concentrations were measured. In the first part of the study, epidural catheters were inserted in 14 patients before herniotomy. Mepivacaine, 1.5 per cent (0.35 ml·kg^{-1}), was administered and norepinephrine (5 μg·ml^{-1}) was added in seven patients. The duration of anaesthesia was prolonged from 54 ± 11 min to 83 ± 12 min ($P < 0.05$) and CSF NE concentrations increased from 68 ± 12 pg·ml^{-1} to 336 ± 85 pg·ml^{-1} in the NE group ($P < 0.01$). In the second part, eight patients with herpetic neuralgia received epidural analgesia at the fourth to eighth thoracic interspace, using bupivacaine 0.25 per cent, with and without NE. The CSF NE concentrations in this group were greater than in the surgical patients before operation and increased from 254 ± 58 to 406 ± 58 pg·ml^{-1} 30 min after administration of bupivacaine with NE. The duration of pain relief was prolonged with NE. These results suggest that adding NE to local anaesthetics prolongs epidural analgesia. Moreover, NE concentrations in surgical patients increased to levels similar to those found in patients suffering from herpetic analgesia. This suggests that the increase of CSF NE in chronic pain states has an antinociceptive effect.

Cette étude a été faite afin de déterminer si l'addition de la norépinéphrine aux anesthésiques locaux prolonge l'analgésie épidurale chez l'homme. En plus, les concentrations de norépinéphrine (NE) du liquide céphalorachidien ont été mesurées. Dans la première partie de l'étude, les cathéters épiduraux ont été insérés chez 14 patients avant herniorraphie. De la mépivacaïne 1,5 pour cent (0,35 ml·kg^{-1}) a été administrée et la norépinéphrine (5 μg·ml^{-1}) a été ajoutée chez sept patients. La durée de l'anesthésie s'est prolongée de 54 ± 11 min. ± 83 ± 12 min. ($P < 0,05$) et les concentrations de NE du liquide céphalorachidien augmentèrent de 68 ± 12 pg·ml^{-1} à 336 ± 85 pg·ml^{-1} dans le groupe norépinéphrine ($P < 0,01$). Dans la deuxième partie, huit patients atteints de neuralgie herpétique ont reçu de l'analgésie épidurale au niveau des quatrième au huitième espaces thoraciques, utilisant la bupivacaïne 0,25 pour cent avec et sans norépinéphrine. Les concentrations de norépinéphrine du liquide céphalorachidien dans ce groupe étaient supérieures à celles des patients chirurgicaux avant l'opération et ont augmenté de 254 ± 58 à 406 ± 58 pg·ml^{-1} 30 min. après administration de bupivacaïne avec norepinéphrine. La durée du soulagement de la douleur était prolongé avec la norépinéphrine. Ces résultats suggèrent que l'addition de norépinéphrine aux anesthésiques locaux prolongent l'analgésie épidurale. De plus, les concentrations de norépinéphrine chez les patients chirurgicaux augmentèrent à un niveau similaire à celui que l'on trouve chez les patients souffrant de neuralgie herpétique. Ceci suggèrent que l'augmentation de la norépinéphrine du liquide céphalorachidien dans les états de douleur chronique amène un effet antinociceptif.

Key words
ANAESTHETIC TECHNIQUE: epidural;
SYMPATHETIC NERVOUS SYSTEM: pharmacology, norepinephrine, CSF concentrations;
INFECTION: herpes zoster.

From the Department of Anesthesiology and Resuscitology, Gunma University School of Medicine, Shouwamachi 3-39-22, Maebashi, Gunma 371, Japan.
Address correspondence to: Dr. F. Goto.

The effects of norepinephrine on the pain inhibitory system in the spinal cord have been studied.[1,2] It has been suggested that catecholamines added to the subarachnoid space not only prolong the duration of the action of local anaesthetics due to vasoconstriction, but also may have a direct effect on the spinal nociceptive system.[3] Therefore the significance of adding catecholamines to prolong spinal and epidural analgesia have been reconsidered both from clinical and basic aspects.[4,5] Recently, it has been shown that clonidine, an alpha-2 adrenergic agonist, produces an antinociceptive effect.[6–8]

However, there is a difference of opinion concerning the effects of adding catecholamines to prolong the duration of local anaesthetics. Caldwell *et al.*[9] reported that phenylephrine prolonged the duration of sensory anaesthesia to a greater extent than epinephrine. In contrast, Concepcion *et al.*[10] reported no difference between the prolongation caused by phenylephrine and

epinephrine. Some questions remain about its clinical value because of the possibility of side-effects caused by ischaemia.[11] An epinephrine concentration of 1 in 200,000 is considered optimal to reduce toxic reactions and potentiate the quality and duration of blockade. However, Urquhart-Hay[12] reported spinal cord infarction following lumbar epidural analgesia and this was attributed to diminished perfusion pressure coupled with vasoconstriction due to epinephrine.

The main endogenous catecholamine in cerebrospinal fluid (CSF) is norepinephrine which is a potent alpha agonist with little beta activity. Thus, we studied the effect of adding norepinephrine to dibucaine in spinal anaesthesia.[13] The data suggested that a small dose (2.5 μg) of norepinephrine was sufficient to prolong the duration of spinal anaesthesia and was more effective than the same dose of epinephrine. But we could not determine the effect of norepinephrine in prolonging spinal anaesthesia at endogenous norepinephrine concentrations in CSF because the free (unconjugated, active type) norepinephrine concentrations in CSF during spinal anaesthesia increased to about 10 $ng \cdot ml^{-1}$, which was more than 100 times the preanaesthetic value (50–110 $pg \cdot ml^{-1}$). This occurred even when a small amount of norepinephrine (less than 1/10 of the normal dose of 2.5 μg) was added to local anaesthetics. Consequently, in this study, we have investigated the effects of adding norepinephrine to epidural anaesthesia on the duration of analgesia and the change of CSF norepinephrine concentrations.

Methods

Two groups of patients were studied. Those in Group I were to undergo herniotomy and those in Group II received epidural analgesia for herpetic neuralgia. The study was approved by our Committee on Human Research. All patients were informed of the nature of the experiment and their written consent was obtained.

In the first study, 14 adult patients (eight males and six females) without pain were studied during unilateral herniotomy. Lactated Ringer's solution was administered at 500 $ml \cdot hr^{-1}$ during the procedure. Epidural catheters were inserted at the first lumbar vertebral space, and 0.35 $ml \cdot kg^{-1}$ of mepivacaine (1.5 per cent) were injected. Half the patients, by random allocation, received local anaesthetic without norepinephrine (Gp-I-C) and half with norepinephrine, 5 $\mu g \cdot ml^{-1}$ (Gp-I-NE). Two ml of CSF were withdrawn through a 23-gauge spinal needle that was inserted at the fourth lumbar vertebral space just before, 15 and 30 min after the administration of the local anaesthetics for epidural anaesthesia. The patients were maintained in a lateral position for 30 min during the CSF collection with the spinal needle still inserted. The duration of anaesthesia was evaluated every ten minutes with ice-cold stimuli. This was continued until the beginning of sensory regression which was defined as a decrease in the level of temperature sensation of two dermatomes. Patients who needed additional drugs for complete anaesthesia and/or for maintaining blood pressure in the operating room were excluded from the study.

In the Group II study, eight patients (five males and three females) suffering from herpes zoster pain in the thoracic region were studied. CSF was withdrawn at the fourth lumbar vertebral space as in Group I. The patients received epidural analgesia with 0.12 $ml \cdot kg^{-1}$ of 0.25 per cent bupivacaine at fourth to eighth thoracic region. Each patient received the analgesia twice with (Group II-NE) or without (Group II-C) norepinephrine from two to four days apart. We measured the pain threshold at the sixth to eighth thoracic vertebral spaces using a heat pain meter (NYT-5, Kudo Electric Co., Ltd.) just before and after epidural analgesia for 30 min.

The pain threshold was determined in an area not affected with herpes zoster. A black paper circle (2 cm in diameter) was placed on the part of the skin to be measured and heat was applied. When the patient felt pain (s)he pushed a button to stop the heating. The pain threshold was the period that the heat was continued. The area measured was gradually moved and assessed three times at each site. The degree of heating was kept at 200 $mcal \cdot sec^{-1} \cdot cm^{-1}$ and the heating period was limited to 12 sec.

The duration of the effects of epidural analgesia in the patients with herpes zoster was based on self-recorded reports using a visual analogue pain scale. The patients recorded the time and pain score when they began to feel slight pain following the analgesia and the time when their pain became as strong as it was before the analgesia. Patients and anaesthetists were unaware of who had received norepinephrine.

The CSF was frozen immediately after withdrawal. Catecholamines were selectively isolated from the samples by activated alumina. The final purification and analysis of the elute for catecholamines was carried out by reverse phase high-liquid chromatography (Waterse Associates, Model 701B) with electron capture detector (Bioanalytical System).[13] An internal standard dihydrobenzylamine (10 ng) was included in the sample to accommodate dilution of CSF and determination of norepinephrine recoveries. The recovery of norepinephrine analysis was 87 ± 5 per cent. Cross-reaction with epinephrine was less than five per cent. Only free norepinephrine was measured.

All results are expressed as means ± SEM. The data were tested for statistical significance using one-way

TABLE I Patient's age, body weight, amount of local anaesthetic, and duration of epidural anaesthesia with (I-NE) and without (I-C) norepinephrine

Group	*Number*	*Age (yr)*	*Weight (kg)*	*Amount of local anaesthetic (ml)*	*Duration (min)*
I-C	7	47.5 ± 3.5	56.8 ± 2.6	20.0 ± 1.5	54 ± 11
I-NE†	7	48.3 ± 5.7	58.7 ± 3.9	21.0 ± 2.2	83 ± 12*

*$P < 0.05$; compared with the data of Group I-C.
†Norepinephrine used in concentration 5 $\mu g \cdot ml^{-1}$.

analysis of variance and paired or unpaired Student's t test. Differences were assumed to be statistically significant when $P < 0.05$.

Results

There were no significant differences with regard to patient age, body weight, or amount of local anaesthetic used during surgery! between Groups I-C and I-NE (Table I).

In Group I-NE, CSF norepinephrine concentrations were increased 15 min after injection of the drugs, and were further elevated at 30 min (Table II). There were no changes in CSF norepinephrine levels in Group I-C. The duration of epidural anaesthesia in Group I-NE was longer than that of Group I-C, $P < 0.05$ (Table I).

Before epidural analgesia the CSF norepinephrine levels of Group II patients were higher than in Group I surgical patients ($P < 0.01$). In Group II-NE, CSF norepinephrine concentrations increased 15 min after epidural analgesia (Table III). Norepinephrine concentrations in CSF in Group II-NE increased more than in Group I-NE at both 15 min and 30 min levels after the administration of local anaesthetic with norepinephrine. The CSF norepinephrine concentrations decreased slightly following analgesia in Group II-C.

The pain threshold increased five minutes after receiving epidural analgesia in both Groups II-NE and II-C ($P < 0.01$) (Table IV). There were no significant differences between the rate of increase of these two groups. The time to return of pain in Group II-NE was longer than in Group II-C ($P < 0.05$) (Table V). In addition, the time until the return of severe pain was almost three times longer ($P < 0.01$) in Group II-NE than in Group II-C.

TABLE II CSF-norepinephrine(NE) concentrations in surgical patients after epidural analgesia with (I-NE) and without (I-C) norepinephrine

			During anaesthesia	
	Group	*Pre-anaesthesia*	*15 min*	*30 min*
CSF-NE	I-C	87 ± 23	90 ± 17	70 ± 15
($pg \cdot ml^{-1}$)	I-NE	68 ± 12	172 ± 37*	336 ± 85†

*$P < 0.05$, †$P < 0.01$, compared with pre-anaesthesia data.

TABLE III CSF-norepinephrine(NE) concentrations in patients with herpes zoster after epidural analgesia with (II-NE) and without (II-C) norepinephrine

			During analgesia	
	Group	*Pre-analgesia*	*15 min*	*30 min*
CSF-NE	II-C	300 ± 89	270 ± 108	215 ± 105
($pg \cdot ml^{-1}$)	II-NE	254 ± 58	358 ± 72*	406 ± 58*

*$P < 0.05$, compared with pre-analgesia data.

Discussion

The main finding of our study was that the addition of norepinephrine prolonged the duration of the analgesia of mepivacaine and bupivacaine in epidural analgesia. For many years, the usefulness and safety of adding vasoconstrictive drugs to epidural anaesthesia have been discussed. The effects of catecholamines on the pain modulating system in the spinal cord have recently attracted attention.[5] It has been suggested that catecholamines added to local anaesthetics prolong spinal anaesthesia, by a direct effect on the spinal analgesic system rather

TABLE IV Changes of pain threshold in patients with herpetic pain after epidural analgesia with (II-NE) and without (II-C) norepinephrine

Group	*Pre-analgesia (sec)*	*5 min after drug administration (sec)*
II-C	3.9 ± 1.3	10.5 ± 1.8*
II-NE	4.8 ± 1.5	8.9 ± 2.1*

*$P < 0.01$, compared with pre-analgesia period.

TABLE V Time until return of herpetic pain after epidural analgesia with (II-NE) and without (II-C) norepinephrine

Group	*Slight pain (hr)*	*Strong pain (hr)*
II-C	2.8 ± 0.9	3.4 ± 0.8
II-NE	5.0 ± 0.7*	10.2 ± 0.8†

*$P < 0.05$, †$P < 0.01$, compared with the data of Group II-C.

than by reducing the spread of local anaesthetics due to their vasoconstriction.[6-8]

Animal studies have demonstrated that analgesia produced by the intrathecal injection of alpha-receptor agonists may be comparable to opiate-induced analgesia.[1,2] Clonidine, a predominantly alpha-2 adrenoceptor agonist, has been shown to have a marked analgetic effect when administered intrathecally.[5-6] Theoretically the pharmacodynamic properties of clonidine would make it a useful adjunct to spinal and epidural analgesia.[5,7,14-15]

Takagi *et al.*[4] reported that electrically induced pain accelerated norepinephrine metabolism. The antinociceptive action of norepinephrine added to the subdural space was confirmed in rats. These reports and the clinical study of Ohno *et al.*[16] support the suggestion that norepinephrine affects the spinal analgesic system in man. But, the effect of added norepinephrine on spinal and epidural anaesthesia has not been assessed clinically as in animal experiments. Also, the action of norepinephrine injected into the epidural space has not been proved. We have confirmed that norepinephrine prolongs the duration of epidural analgesia and anaesthesia, and that it moves into the CSF from the epidural space. The CSF norepinephrine concentrations were higher in patients who suffered from chronic pain than in surgical patients before operation. However, plasma norepinephrine concentrations following the administration of norepinephrine with local anaesthetics were elevated to almost the same range in both groups. These data suggest that norepinephrine potentiates the analgesic action of local anaesthetics on the spinal cord at levels, 100–400 $pg \cdot ml^{-1}$, produced by endogenous secretion in man.

Unfortunately, it is impossible to compare the analgesic potency of norepinephrine with clonidine, because clonidine is not available for this use in Japan. We have studied the effects of the endogenous catecholamine in CSF, norepinephrine, on the duration of local anaesthetics in epidural anaesthesia.

It is difficult to determine whether catecholamine injected into the epidural space penetrates the epidural membrane and passes into the subdural space. When norepinephrine was injected into the lumbar epidural space in Group I-NE, the drug might have spread into the subdural space via the hole made by the needle for CSF collection, but this is unlikely in Group II-NE patients with thoracic epidural analgesia.

There was no significant difference between Group II-C and Group II-NE in the increase of pain threshold due to the addition of NE. The data suggest that the added NE did not alter the onset of local anaesthetic action.

Our study indicated that adding norepinephrine to local anaesthetics prolonged the duration of the action of epidural analgesia. However, these clinical studies contain many problems in speculating upon the aetiology of analgesic methods. In the experiments of Group II, we examined patients with the same kind of disease and further compared the results of patients receiving epidural analgesia with and without norepinephrine. The influences of patients' conditions, such as age, sex, and disease, were neglected. The data confirmed that the addition of norepinephrine to local anaesthetics prolonged the duration of epidural analgesia. This was achieved at CSF norepinephrine concentrations which were similar to the endogenous levels produced in the presence of pain, such as herpetic neuralgia.

References

1 *Kuraishi Y, Harada Y, Takagi M.* Noradrenaline regulation of pain-transmission in the spinal cord mediated by alpha adrenoceptors. Brain Res 1979; 174: 333–6.

2 *Reddy SVR, Yaksh TL.* Spinal noradrenergic terminal system mediates antinociception. Brain Res 1980; 189: 391–401.

3 *Bromage PR, Camporesi EM, Durant PA, Nielsen CH.* Influence of epinephrine as an adjuvant to epidural morphrine. Anesthesiology 1983; 58: 257–62.

4 *Takagi H, Shiomi H, Kuraishi Y, Fukui K, Ueda H.* Pain and the bulbospinal noradrenergic system: pain-induced increase in normetanephrine content in the spinal cord and its modification by morphine. Eur J Pharmacol 1979; 54: 99–107.

5 *Kitahata LM.* Spinal analgesia with morphine and clonidine. Anesth Analg 1989; 68: 191–3.

6 *Spaulding TC, Venafro JJ, Ma MG, Fielding S.* The dissociation of the antinociceptive effect of clonidine from supraspinal structures. Neuropharmacology 1979; 18: 103–5.

7 *Tamsen A, Gordh T.* Epidural clonidine produces analgesia. Lancet 1984; 2: 231–2.

8 *Bedder MD, Kozody R, Palahniuk RJ, Cumming MO, Pucci WR.* Clonidine prolongs canine tetracaine spinal anaesthesia. Can Anaesth Soc J 1986; 33: 591–6.

9 *Caldwell C, Nielsen C, Baltz T, Taylor P, Helton B, Butler P.* Comparison of high-dose epinephrine and phenylephrine in spinal anesthesia with tetracaine. Anesthesiology 1985; 62: 804–7.

10 *Concepcion M, Maddi R, Francis D, Rocco AG, Murray E, Covino BG.* Vasoconstrictors in spinal anesthesia with tetracain-A comparison of epinephrine and phenylephrine. Anesth Analg 1984; 63: 134–8.

11 *Harrison PD.* Paraplegia following epidural analgesia. Anaesthesia 1975; 30: 778–82.

12 *Urquhart-Hay D.* Paraplegia following epidural analgesia. Anaesthesia 1969; 24: 461–70.

13 *Goto F, Fujita N, Fujita T.* Cerebrospinal fluid catecholamine levels and duration of spinal anaesthesia. Can J Anaesth 1988; 35: 157–61.
14 *Frumin MJ.* The appearance of procaine in the spinal fluid during peridural block in man. J Pharmacol Exp Ther 1953; 109: 102–5.
15 *Bromage PR.* Epidural pressure. *In*: Bromage PR (Ed.). Epidural Analgesia. Philadelphia: Saunders W.B., 1978; 160–74.
16 *Ohno T, Miyoshi Y, Yukinari T, Haseda S, Gotoh Y.* Pain and noradrenaline concentration in cerebrospinal fluid. Japanese Journal of Anesthesiology 1983; 32: 183–91.