Regional Anesthesia and Pain

Epidural anesthesia with lidocaine reduces propofol injection pain

[L'anesthésie péridurale avec lidocaïne réduit la douleur provoquée par l'injection de propofol]

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Purpose: To determine whether epidural lidocaine reduces the severity of propofol injection pain compared with *iv* lidocaine.

Methods: A prospective, randomized double-blind clinical study was conducted in 120 female patients scheduled for elective gynecological laparotomy. A lumbar epidural catheter and an *iv* catheter placed in the cephalic vein of the non-dominant hand were used in all patients. Patients of the control group (Group C) were given epidural normal saline followed by *iv* normal saline then *iv* propofol. Patients of Group E were given epidural 2% lidocaine (0.08 $mL \cdot cm^{-1}$) followed by *iv* normal saline and then propofol. Patients of Group V were given epidural normal saline followed by *iv* 2% lidocaine (0.05 $mL \cdot kg^{-1}$) then propofol. Pain was scored as no pain=0, minimal pain=1, moderate pain=2, severe pain=3.

Results: The pain scores, in group E; 1 (0–2) and group V; 2 (0–2), were significantly lower than in group C; 2 (1–3); median (25^{th}–75^{th} percentile) ($P < 0.001$). There was no difference in pain score between groups E and V. The plasma lidocaine concentration 15 min after epidural lidocaine was $2.74 \pm 0.54\ \mu g \cdot mL^{-1}$, compared with $1.54 \pm 0.31\ \mu g \cdot mL^{-1}$ at three minutes after *iv* lidocaine.

Conclusion: Epidural and *iv* lidocaine equally reduced the severity of propofol injection pain despite higher lidocaine plasma concentrations in epidurally administered lidocaine.

Objectif : *Déterminer si la lidocaïne, en injection péridurale comparée à l'injection iv, peut réduire la douleur causée par l'administration de propofol.*

Méthode : *L'étude clinique, prospective, randomisée et à double insu, a été menée auprès de 120 femmes pour qui une laparotomie gynécologique avait été prévue. Un cathéter péridural lombaire et un cathéter iv, introduit dans la veine céphalique de la main la moins utilisée, ont été employés chez toutes les patientes. Dans le groupe témoin T, on a administré un soluté physiologique par voie péridurale, puis iv, suivi de propofol iv. Dans le groupe P, on a donné de la lidocaïne à 2 % (0,08 $mL \cdot cm^{-1}$ péridurale, puis un soluté physiologique et du propofol iv. Dans le groupe V, on a donné un soluté physiologique péridural suivi de lidocaïne iv à 2 % (0,05 $mL \cdot kg^{-1}$) et de propofol. La douleur a été cotée comme suit : 0 = aucune douleur, 1 = douleur minimale, 2 = douleur modérée, 3 = douleur sévère.*

Résultats : *Dans les groupes P, 1 (0–2) et V, 2 (0–2), les seuils de douleur ont été significativement plus bas que ceux du groupe T, 2 (1–3); médiane (25^{e}–75^{e} percentile) ($P < 0,001$). Les scores n'étaient pas différents entre les groupes P et V. La concentration plasmatique de lidocaïne, 15 min après l'injection péridurale, était de $2,74 \pm 0,54\ \mu g \cdot mL^{-1}$, comparé à $1,54 \pm 0,31\ \mu g \cdot mL^{-1}$ trois minutes après l'injection iv de lidocaïne.*

Conclusion : *L'administration péridurale et iv de lidocaïne réduit également la sévérité de la douleur causée par l'injection de propofol malgré de plus fortes concentrations plasmatiques de lidocaïne péridurale.*

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PAIN during injection of propofol remains a clinical problem. Our clinical experience suggests that lumbar epidural anesthesia with lidocaine 2% diminishes propofol injection pain, when the latter is administered after analgesia is established, 15 min postepidural lidocaine administration. In the present study, we investigated whether epidural lidocaine reduces the severity of pain during propofol injection with *iv* lidocaine and measured plasma lidocaine.

Methods

The study protocol was approved by the Human Ethics Review Committee of Nippon Medical School and a signed consent was obtained from each subject. The study included 120 consecutive female patients, ASA I or II, aged 30–60 yr, undergoing elective gynecological laparotomy. None of the patients received premedication. Patients taking sedatives or analgesic agents and those with neurological or cardiovascular involvement were excluded from the study.

Following injection of a small dose (<2 mL) of procaine hydrochloride 1% for local anesthesia, the epidural space was punctured using the loss-of-resistance technique with normal saline at the L2–3 intervertebral space by a paramedian approach. An epidural catheter was inserted and its tip placed 4–5 cm cephalad.

An 18-gauge Teflon® cannula (Insyte-W™ Vialon™ E, Becton Dickinson, NJ) was inserted into the cephalic vein of the non-dominant hand, without the use of local anesthetic, early in the morning (about three hours before the induction of anesthesia) in the ward on the day of surgery and *iv* infusion of lactate Ringer's solution was started.

For arterial pressure monitoring and blood sampling, a 20-gauge Teflon® cannula (Insyte-W™ Vialon™ E, Becton Dickinson) was inserted into the radial artery on the forearm contralateral to the venous line, following injection of a minimal dose (<1 mL) of procaine hydrochloride 1% for local anesthesia.

Patients were randomly allocated into one of three groups (C, E and V). Normal saline (0.08 $mL \cdot cm^{-1}$ body height) was administered epidurally in patients of group C (control group, n=40), followed 12 min later by *iv* injection of normal saline (0.05 $mL \cdot kg^{-1}$). Three minutes later, propofol (2.5 $mg \cdot kg^{-1}$) was injected through the same (cephalic) vein used for injection of normal saline.

Lidocaine 2% (0.08 $mL \cdot cm^{-1}$) was administered epidurally in patients of group E (n=43). This was followed, 12 min later, by *iv* injection of normal saline, and three minutes later by injection of propofol at a dose similar to that used for group C. Analgesia in patients of group E was confirmed with the pinprick test 15 min after epidural administration of lidocaine.

Normal saline (0.08 $mL \cdot cm^{-1}$ body height) was injected epidurally in patients of group V (n=37). This was followed 12 min later by *iv* injection of 2% lidocaine (0.05 $mL \cdot kg^{-1}$), and three minutes later by propofol through the same vein as lidocaine.

Injection of lidocaine or normal saline into the epidural space was performed using a syringe pump (STC 525™, Terumo, Japan) at a rate of 400 $mL \cdot hr^{-1}$. The dose of lidocaine was less than the recommended dose for ventricular arrhythmias and possible side-effects were explained in advance. Propofol was kept in an incubator set at 20–23°C until just before administration. In the operating theatre, after setting conventional monitors and cannulating the radial artery, propofol was administered through a three-way stopcock directly connected to the cannula inserted into the cephalic vein, with the *iv* infusion line closed, using an electric-powered syringe pump (Graseby Anaesthesia Pump 3500™, Graseby Medical, UK). The rate of injection was 3 $mg \cdot kg^{-1} min^{-1}$ and the total dose was 2.5 $mg \cdot kg^{-1}$.

The severity of pain during injection of propofol was rated using a four-point scale. It was considered to be too difficult for the patient to express the injection pain using complex terms within a short period during induction of anesthesia. Accordingly, before the administration of lidocaine, the patient was asked to evaluate pain during the injection of propofol and, when present, grade it as mild="grade 1", moderate="grade 2 ", or severe="grade 3", as used in previous reports.[1–7] Absence of pain was scored as "grade 0". In each patient, the maximum degree of pain before falling asleep was recorded as the pain score. The time point when evaluating pain score was also recorded. In patients with pain score "0", "the time point" was recorded as 50 sec, representing the total period required for the injection of propofol.

Arterial blood samples were obtained at 30 sec, one, two, three, five, seven, ten, 15 and 30 min after epidural lidocaine and at 30 sec, one, two, three and five minutes after *iv* lidocaine, to determine the plasma lidocaine concentrations. Blood samples were collected from the arterial cannula.

After induction of anesthesia, the lungs were ventilated mechanically with 30–50% oxygen in air through an endotracheal tube, in combination with epidural and continuous *iv* anesthesia using propofol. We administered epidural analgesia postoperatively with a combination of local anesthetics and opioids. The relationship between the pain score and the level of analgesia was analysed for group E. We also analysed

TABLE Demographic data of the three groups

	Group C	*Group E*	*Group V*	*P value*
No. of patients	4 0	4 3	37	
Age (yr)	42.8 ± 6.7	43.5 ± 8.8	46.4 ± 5.9	NS
Height (cm)	157.2 ± 5.3	155.4 ± 5.4	154.5 ± 5.0	NS
Weight (kg)	53.6 ± 11.2	55.4 ± 6.4	53.7 ± 7.6	NS
ASA grade I/II (*n*)	24/16	21/22	18/19	NS

Group C received epidural normal saline followed by *iv* normal saline, then propofol. Group E received epidural lidocaine followed by *iv* normal saline, then propofol. Group V received epidural normal saline followed by *iv* lidocaine, then propofol. Values for age, height and weight are mean ± SD. There were no significant differences (NS) among the three groups.

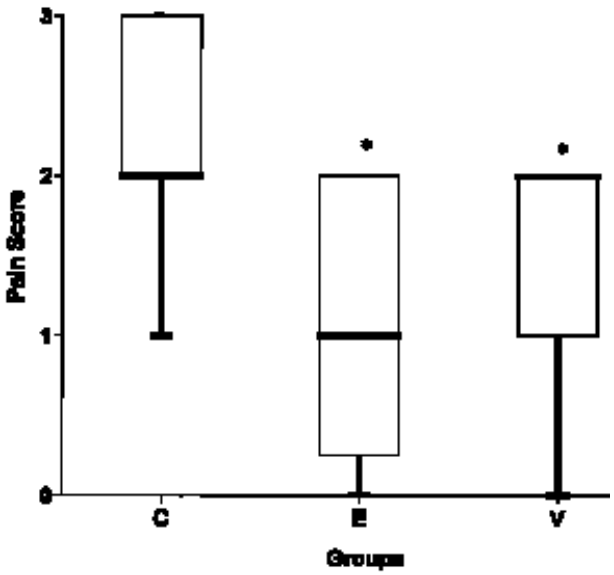

FIGURE 1 Pain scores during injection of propofol in the three groups. The lower and upper borders of each box show the 25th and 75th percentiles, respectively. The thick horizontal line shows the median, marking the 50th percentile. The vertical error bars show the 10th percentile. Pain scores of groups E and V were significantly lower than that in group C. There was no significant difference in pain scores between group E and group V. * P <0.001 *vs* group C.

the relationships between the pain score and plasma lidocaine concentrations at 15 min after epidural lidocaine, and those between pain score and plasma lidocaine concentrations at three minutes after *iv* lidocaine. Plasma lidocaine levels were measured using an automated analyser (TDX™, ABBOTT, IL) with fluorescence polarization immunoassay.[8] The detection range of lidocaine by this method is 0.1–10 $\mu g \cdot mL^{-1}$, according to the specifications provided by the manufacturer.

Data are reported as mean ± SD. Differences in age, body weight, body height and plasma lidocaine concentrations among the three groups were examined for statistical significance by using one-way analysis of variance (ANOVA). Differences in ASA status among groups was analysed with the chi-square test and those for pain score with the Kruskal-Wallis test followed by post-hoc Dunn's multiple comparison test (GraphPad PRISM™ version 3.02, GraphPad Software, San Diego, CA). The relationship between the pain score and time of pain evaluation, that between pain score and analgesic levels, and between pain score and plasma lidocaine concentrations were analysed with Spearman's correction coefficient by rank. The relationship between pain score and "time points" was analysed excluding patients with the pain score "0" because there were no patients in group C with pain score "0". P <0.05 was regarded as significant. DeltaGraph® 4.03J for Windows™ (DeltaPoint®, Japan Polaroid Computing) was used for illustrations.

Results

There were no differences in age, body weight, body height or ASA status among the three groups (Table). Serious symptoms or signs related to *iv* lidocaine were not observed. However, 10% of patients developed mild symptoms. These consisted of feeling of fullness in the ear in four patients and tinnitus in three patients.

The median pain scores in groups E and V were lower than that in group C (P <0.001). There was no difference in the pain score between group E and group V, as shown in Figure 1.

Plasma lidocaine concentrations in group E increased progressively after epidural injection of the agent and reached a peak value (2.73 ± 0.54 $\mu g \cdot mL^{-1}$) at 15 min after administration, which was significantly higher than that at 30 min (2.12 ± 0.56 $\mu g \cdot mL^{-1}$) as shown in Figure 2A. In group V, plasma lidocaine concentrations at three minutes after *iv* injection was 1.58 ± 0.31 $\mu g \cdot mL^{-1}$ (Figure 2B), which was significantly lower than in group E (P <0.001).

The correlation coefficient (r value) of the relationship between pain score and time point when evaluating pain score was 0.2 in group C, 0.5 in group E and 0.5 in group V (Figures 3A, B and C). The correlation coefficient of the relationship between pain score and number of dermatomes blocked in group E 15 min after epidural lidocaine was 0.02 (Figure 4). The correlation coefficient of the relationship between pain score and plasma lidocaine concentrations was 0.07 in group E (Figure 5A), and 0.03 in group V (Figure

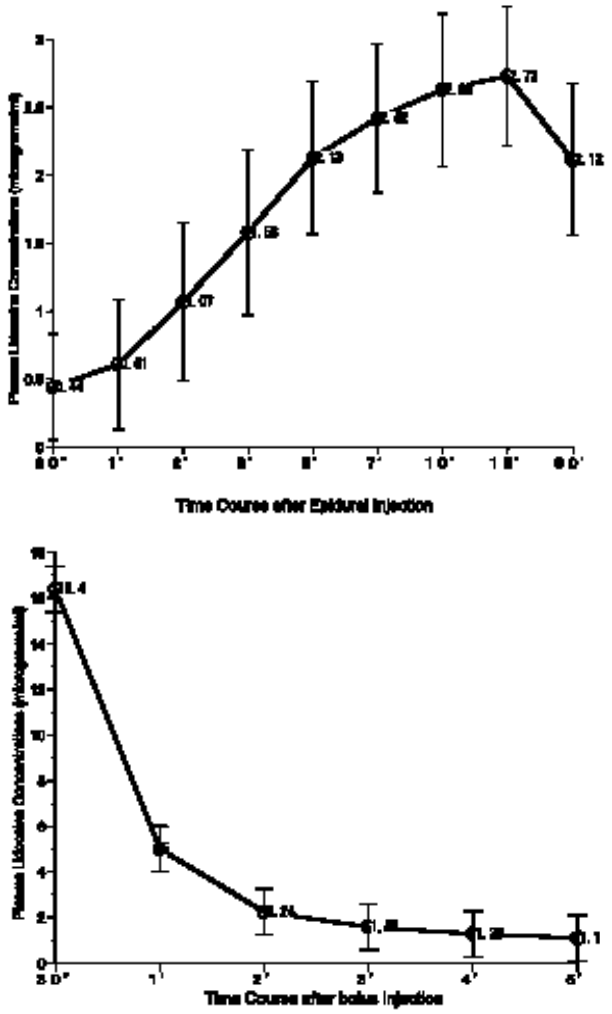

FIGURE 2 A, Plasma lidocaine concentrations in patients of group E. Note the gradual increase and peak value at 15 min after epidural administration of 2% lidocaine; B, Plasma lidocaine concentrations in patients of group V. Note the gradual fall after *iv* administration of 2% lidocaine.

5B). There were no significant relationships between the pain score and time point when evaluating pain score, between the pain score and number of dermatomes blocked, or between the pain score and plasma lidocaine concentrations.

Discussion

The major finding of the present study is that propofol-related pain was significantly reduced after either *iv* or epidural injection of lidocaine, despite higher lidocaine plasma concentrations in patients with epidurally administered lidocaine.

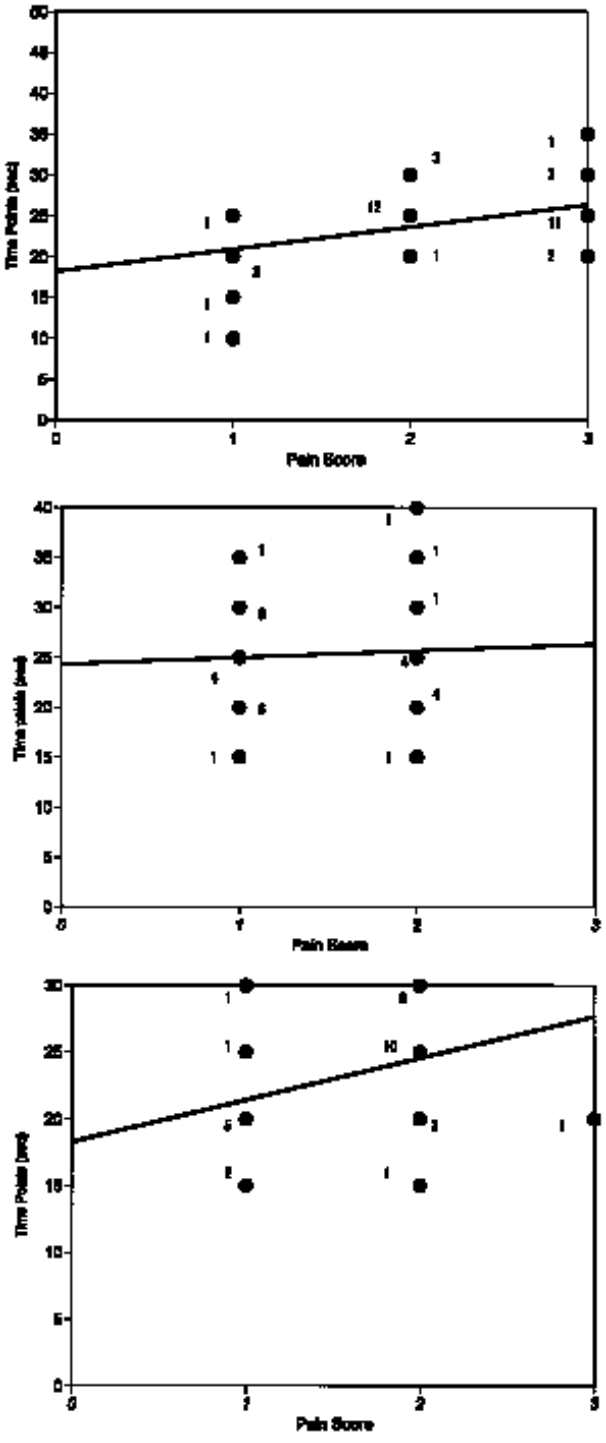

FIGURE 3 A, Relationship between pain score and the time of pain score evaluation in group C; B, Relationship between pain score and the time of pain score evaluation in group E; C, Relationship between pain score and the time of pain score evaluation in group V. Numbers close to the solid circles represent the number of patients for each symbol.

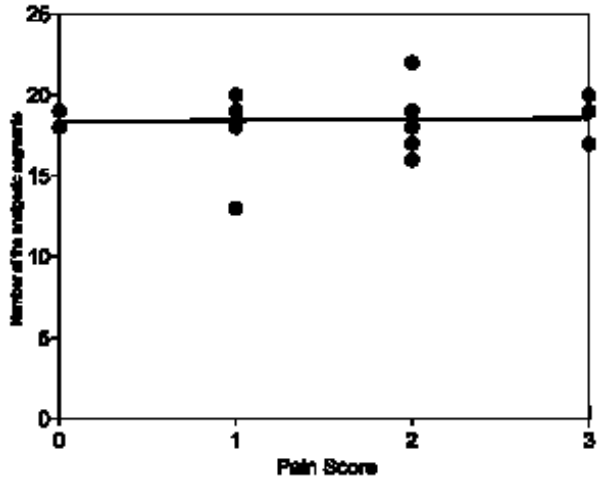

FIGURE 4 Relationship between the number of analgesic dermatomal segments evaluated 15 min after epidural injection of lidocaine and plasma lidocaine concentrations in group E.

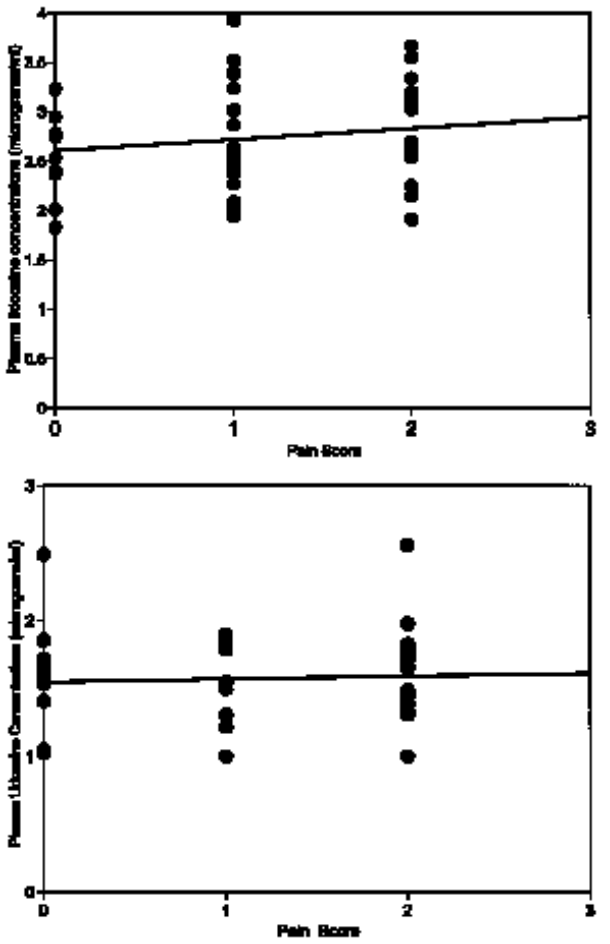

FIGURE 5 A, Relationship between pain score and plasma lidocaine concentrations 15 min after epidural injection of lidocaine in group E; B, Relationship between pain score and plasma lidocaine concentrations three minutes after *iv* injection of lidocaine in group V.

Among the various approaches used to reduce propofol injection pain is the use of lidocaine. Lidocaine is administered either mixed with propofol or prior to injection of propofol. There is some evidence to suggest that the analgesic effects of the former technique may be more effective than the latter.[9,10] However, mixing of propofol emulsion with other drugs is not recommended by the manufacturer,[11] because of possible changes in emulsion stability. Thus, the common practice of mixing lidocaine to propofol to reduce pain on injection should be considered carefully.[11] Picard and Tramer[12] used lidocaine (0.5 $mg \cdot kg^{-1}$) intravenously with a rubber tourniquet on the forearm 30 to 120 sec before propofol injection. They suggested that the "tourniquet method" is the most efficacious procedure to reduce propofol injection pain. Manger and Holak[13] also demonstrated that application of a tourniquet inflated at a pressure of 50 mmHg followed by *iv* lidocaine (5 mL or 100 mg of lidocaine 2%) diminished hand pain associated with subsequent propofol injection. However, even though they reported the lack of any symptoms using this technique, it is possible that the rapid flow of 100 mg of lidocaine into the systemic circulation after the release of tourniquet might produce serious-side effects.

Picard and Tramer[12] reviewed the results of using 15 different pharmaceutical agents by analysing 12 different physiological variables, in order to analyse the most appropriate techniques to reduce the incidence and severity of propofol injection pain. They concluded that injection of lidocaine/propofol and use of the tourniquet method were associated with the least pain. Several studies have examined the cause of propofol pain and the mechanisms of pain alleviation by various therapeutic techniques. Scott *et al.*[9] suggested that propofol injection pain results from activation of the kinin cascade system and that lidocaine acts as a stabilizer of this system, preventing the release of pain-related mediators. When using the "tourniquet method", lidocaine held in the vein for a certain period of time results in anesthesia of the vein.[13] Therefore, the efficacy of *iv* lidocaine should be higher with a tourniquet.

Propofol is presented in emulsion form due to its low water solubility. The emulsion droplets are less than 1 μm in diameter.[11] Nathanson *et al.*[5] demonstrated

immediate changes in the stability of propofol emulsion when 10–20 mg of lidocaine solution is added to 200 mg propofol. However, the changes in droplet size of propofol emulsion following the addition of <20 mg lidocaine to 200 mg propofol (final lidocaine concentration, 0.95%), are unlikely to be of clinical importance. An increase in the droplet size to >5 μm poses the risk of pulmonary fat embolism.[14,15] In this regard, Ho and colleagues[16] reported that the optimal concentration of lidocaine that reduced pain on injection of a propofol-lidocaine mixture was 0.1%. This concentration is within the acceptable range suggested by Nathanson *et al.*[5] The mechanism explaining the efficacy of this technique we used remains unclear.[11]

Although *iv* lidocaine without a tourniquet prior to propofol injection, our results show that the analgesic effect of epidural lidocaine was not significantly different from that of *iv* bolus injection of lidocaine and the pain score after propofol injection was reduced to a similar level in both methods. The analgesic effects of epidural lidocaine on pain during injection of propofol might be explained by the following mechanisms: (a) a direct effect of epidural anesthesia; (b) the systemic effect of lidocaine following absorption from the epidural space. Furthermore, the effects of epidural lidocaine are likely to represent the central sedative effects of spinal deafferentation and involvement of the spinal cord in systemic analgesia. In our study, the level of analgesia did not exceed the level of T5, there were no signs of sympathetic nerve block in the upper extremities, and there was no significant relationship between the pain score and the level of analgesia. In group E, since lidocaine acted epidurally as well as systemically, the analgesic effect on pain during propofol injection should have been greater in these patients compared to those of group V. However, analysis of the pain scores showed no difference between the two groups.

In conclusion, the present study shows that lidocaine epidural anesthesia reduces pain during propofol injection. We also confirmed, in another group of patients, that pre-treatment with *iv* lidocaine reduces propofol-related pain. Both methods are useful to lessen propofol injection pain when the latter is used for the induction or maintenance of anesthesia. Our results also indicate that it is unnecessary to use *iv* lidocaine to prevent pain on injection of propofol when patients are scheduled to receive epidural lidocaine anesthesia. Further studies are necessary to investigate the pain reducing mechanism of epidural lidocaine.

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