Long-term effect of epidural injection with sustained-release lidocaine particles in a rat model of postoperative pain

T. Suto, H. Obata, M. Tobe, H. Oku, H. Yokoo, Y. Nakazato and S. Saito

Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22, Showa, Maebashi, Gunma 371-8511, Japan
Department of Human Pathology, Gunma University Graduate School of Medicine, 3-39-22, Showa, Maebashi, Gunma 371-8511, Japan
Department of Chemistry and Chemical Biology, Gunma University Graduate School of Engineering, Gunma, Japan
* Corresponding author. E-mail: hobata@gunma-u.ac.jp

Background. Single applications of sustained-release local anaesthetics may provide prolonged pain relief without requiring indwelling catheters, but have not yet been investigated for epidural postoperative pain management. We synthesized injectable sustained-release lidocaine particles (SRLPs) from biodegradable polymers and examined their effect in a rat model of postoperative pain.

Methods. Two types of polylactic acid particles, SRLP-10 and SRLP-25, containing 10% or 25% lidocaine, respectively, were generated and the lidocaine release was evaluated in vitro for 14 days. The SRLPs were then injected epidurally in the male Sprague–Dawley rats immediately before they received a hindpaw incision (the postoperative pain model), and hindpaw hypersensitivity was evaluated with the von Frey test. Motor paralysis and coordination were also assessed using a paralysis score and rota-rod test. Neurotoxicity and inflammation of the spinal cord, cauda equina, and tissue surrounding the injection site were histologically evaluated.

Results. In vitro, SRLP-10 and SRLP-25 released lidocaine over 7 and 3 days, respectively. The in vivo injection of SRLP-10 (80 mg) produced anti-hypersensitivity with no evidence of motor paralysis for 7 days after the paw incision, and SRLP-25 (60 mg) inhibited postoperative hypersensitivity for 7 days. Temporary motor paralysis (15 min) was observed after the injection of SRLP-25 (even with 40 mg). Foreign body reactions were observed around the SRLP injection site at 1 and 4 weeks after injection. No histopathological changes were observed at 1 or 4 weeks.

Conclusions. The epidural injection of SRLPs produced prolonged anti-hypersensitivity in a rat model of postoperative pain with no major complications.

Keywords: epidural; hypersensitivity; postoperative pain; rats

Accepted for publication: 25 May 2012

The management of postoperative pain improves postoperative outcomes and patient satisfaction. The aggressive management of acute postoperative pain with pre-emptive and multimodal analgesia may reduce chronic postoperative pain. Epidural analgesia is widely used for postoperative pain management, and prolongation of the effect of the local anaesthetic may provide long-term analgesia without requiring the insertion of an indwelling catheter. Sustained-release versions of various local anaesthetics have been produced previously in various forms, in particular, prolonged analgesic effects in animals and humans have been reported with sustained-release bupivacaine.

Lidocaine is widely used as a local anaesthetic drug because it has a wide safety margin for cardiac toxicity, and several sustained-release lidocaine formulations have been produced. The anaesthetic effects of sciatic nerve block, epidural block, or local analgesia by sustained-release lidocaine have been examined in normal animals. The efficacy of a sciatic nerve block with sustained-release lidocaine was also examined in a rat model of postoperative pain. However, epidural injection with sustained-release lidocaine has not yet been evaluated for the treatment of postoperative pain. In the present study, we produced injectable sustained-release particles by loading 10% (w/w) and 25% lidocaine into a biodegradable polymer (polylactic acid, PLA), and we examined the efficacy of a single epidural treatment of the particles in a rat model of postoperative pain.
Methods

Drug preparation

Sustained-release lidocaine particles (SRLPs) loaded with 10% lidocaine (SRLP-10) were prepared by dissolving lidocaine (30 mg) and PLA (270 mg, molecular weight 20,000, Wako Pure Chemical Industries Ltd, Osaka, Japan) in 100% chloroform (2.0 ml, density 1492 mg ml⁻¹, Sigma, St Louis, MO, USA), and then pouring the solution onto circular glass plates (90 mm diameter). The lidocaine/PLA/chloroform solution was incubated for 7 days at 25 °C to allow the chloroform solution to evaporate. When the solvent evaporated, a thin membrane formed. The membrane was removed from the glass plate after 5 days with a spatula. The membrane fragments were ground with a mortar for 1.5 min at -15 °C. The resulting SRLP-10 was then used for the experiments in doses of 40 or 80 mg.

For the SRLP-25 particles, 75 mg of lidocaine and 225 mg of PLA were prepared in 2 ml of chloroform. Chloroform was evaporated as described above. The resulting membrane was removed after 5 days and ground with a mortar for 3 min at -15 °C. The resulting SRLP-25 particles were used for the experiments at doses of 40 or 60 mg.

Characterization of SRLPs

The morphology and surface appearance of the SRLPs were examined via scanning electron microscopy (SEM) on a JEOL JSM-5500 (JEOL Ltd, Tokyo, Japan) operating at 15 kV. Before SD observation, the particles were placed on a stage and sputter-coated with carbon. The average diameter was calculated from the microscopic digital images (light microscope, magnification ×100) using image analysis software (ImageJ 1.44o, NIH, Bethesda, MD, USA).

Lidocaine content

The actual lidocaine content in the SRLP-10 and SRLP-25 particles was determined by weighing the SRLPs (around 10 mg) and then dissolving them in 1 ml of 1 N sodium hydroxide solution (Wako Chemical, Japan) to facilitate hydrolytic degradation. The solution was incubated for 7 days at 37 °C until the SRLPs were completely dissolved. The solution was neutralized with hydrochloric acid and diluted by adding phosphate-buffered saline (PBS) up to 10 ml. The lidocaine concentration of the solution was measured by SRL Inc. (Maebashi, Japan) using a fluorescence polarization immunoassay. The actual lidocaine content in the SRLPs was calculated from the concentration and the weight.

In vitro lidocaine-release rate study

SRLPs (around 10 mg) and 0.1 M PBS (2 ml) were placed in dialysis membrane tubing (18 mm width, 60 mm length, MWCO 3500; Spectrum Laboratories Inc., Dominguez, CA, USA), and both ends of the tubing were closed with a 3-0 silk suture. The tubing including SRLPs dispersed in PBS was placed into a glass cylinder filled with PBS (40 ml) and incubated at 37 °C. PBS was prepared from monobasic phosphate (12.69 g) and dibasic phosphate (43.74 g) in 4 litre of distilled water. We obtained 0.3 ml samples from the glass cylinder at predetermined time points and made up the loss with PBS. The lidocaine concentration in each sample was measured using a fluorescence polarization immunoassay.

Animals

This investigation was approved by the Animal Care and Use Committee of Gunma University Graduate School of Medicine (No. 09-33, Maebashi, Japan). The male Sprague–Dawley rats weighing 250–300 g were used in all experiments. The rats were allowed free access to food and water and maintained on a 12 h light–dark cycle. In total, 112 rats were used. Six rats were excluded from the study because of a failure of drug administration (cerebrospinal fluid was seen during the procedure in three rats, and SRLPs seeped from the epidural space in three rats). Thus, the data from 106 rats were included in the analysis. Animals that were not used for histopathological studies were immediately killed after the behavioural experiments by injecting an overdose of sodium pentobarbital.

Epidural drug application

Animals were anaesthetized with isoflurane (4% to induce and 2% to maintain) in 100% oxygen, and adequate anaesthesia was ascertained by the pedal withdrawal response. After the skin on the back of the rat was incised, the subcutaneous tissue and muscle under the skin were dissected and separated to expose the spinous process of the fifth lumbar vertebra, and the spinous process was removed to expose the L4/L5 interspinal ligament. The ligament was gently removed with a fine needle until the space under the caudal edge of the fourth lumbar vertebra was visualized, and the drug was gently injected into the space with an 18 G catheter. When clear fluid was observed to come from the space under the caudal edge of the fourth lumbar vertebra before or after the injection, we considered that the catheter had reached the subdural space, and the rat was excluded from behavioural testing. The catheter was removed, and the muscle, fascia, and skin were closed with 3-0 silk.

In all behavioural experiments, the SRLPs were dispersed in 0.4 ml of normal saline with 0.01% (v/v) surfactant (Tween 80). As control group, the PLA in 0.4 ml of normal saline with 0.01% (v/v) surfactant was used. The lidocaine solution used in the ‘lidocaine 2 mg group’ for behavioural experiments was prepared by dissolving 2.2 mg of lidocaine hydrochloride in 0.4 ml of normal saline with 0.01% Tween 80.

Postoperative pain model

A postoperative pain model was produced by a hindpaw incision as described by Brennan and colleagues. The paw incision was made immediately after the epidural injection procedure. In this model, a 1 cm incision was made on the plantar surface of the left hind paw during isoflurane anaesthesia. The incision was started immediately distal to the heel and extended to a point just proximal to the first set
of footpads. The plantaris muscle was elevated using forceps and incised longitudinally. The wound was closed with two mattress sutures using 5-0 silk. After surgery, the rats recovered from the anaesthesia in their cages. The wounds were checked for evidence of dehiscence before behavioural testing. The person performing the behavioural tests was blinded to the drug administration.

**von Frey's test**

Rats were placed in individual plastic chambers with a plastic mesh floor and allowed to adjust to the environment for 30 min (15 min for the first post-surgery test). The mechanical withdrawal threshold was determined using an electronic von Frey anaesthesiometer (IIUC Inc., Life Science Instruments, Woodland Hills, CA, USA). The polypropylene tip was fixed to the handheld pressure transducer, and the tip was applied perpendicularly to the area adjacent to the wound with a gradual increase in pressure. The force needed to elicit the withdrawal of the hindpaw was automatically recorded as a threshold in grams by the pressure transducer. Stimulations were performed 10 times for each rat at ~1 min intervals, and the mean value of the 10 readings was used for the analysis as the individual threshold. Stimulations were performed before (pre) and after the hindpaw incision (30 min, 2, 6 h, 1, 2, 5, and 7 days after injection). Test stimulations to allow the rats to become used to the test were performed for 2 days before the data collection.

**Pinprick test**

A 75 mm, 24 G pencil point spinal needle (Unisis Corporation, Saitama, Japan) was used to provide noxious stimulation. The needle was gently and perpendicularly applied to the hindpaw, and the withdrawal response was scored as follows: 0=rapid escape or vocalization; 1=delayed escape; 2=no response. Three stimulations were performed and the average score was recorded for each time point before (pre) and after epidural administration (2, 6 h, 1, 2, 5, and 7 days).

**Paralysis**

Weakness of the skeletal muscle tone after epidural drug administration was evaluated by manual manipulation and visual observation, and it was scored as follows: 0=normal tone, free movement of the hindpaws; 1=weak hypotonia of the hindpaws on manual manipulation/almost normal posture; 2=moderate hypotonia of the hindpaws/movement in the hindpaws, inability to support the body; and 3=complete paralysis/no movement in the hindpaws, flat body posture.

The effect of the SRLPs on gait coordination was evaluated by a rota-rod (ENV-577, Med Associates) test. Two days before the data collection, the rats used for this test received three training sessions. After the training, the rats were tested on the rota-rod treadmill with increasing speeds starting at 4 rpm, and the latency to fall from the rod was recorded for each trial. Paralysis scores and rota-rod latencies were evaluated for each time point before (pre) and after epidural administration (15, 30, 45 min, 1, 2, 6 h, 1, 2, 5, and 7 days).

**Histopathology**

To assess the histopathology, we excised the spinal cord and cauda equina near the injection site 1 week after drug administration. Three animals were selected from the lidocaine 2 mg-treated group, the SRLP-10 (80 mg)-treated group, the SRLP-25 (60 mg)-treated group, and the control group (PLA 60 mg). The other three rats from each group were used for histopathological assessment at 4 weeks after the drug administration. The rats from each group were deeply anaesthetized with an intraperitoneal injection of sodium pentobarbital (100 mg kg⁻¹) and perfused through the aorta with 0.01 M PBS at 4 °C containing 1% sodium nitrate, followed by 500 ml of 4% paraformaldehyde in 0.1 M PBS. A laminectomy was then performed to expose the spinal cord and cauda equina. The spinal cord and cauda equina from 1 cm above to 1 cm below the L4/L5 interspace were carefully removed and fixed overnight in 0.1 M phosphate-buffered 4% paraformaldehyde. Serial dehydration with graded ethanol and xylene was followed by embedding in paraffin. Tissue sections (3 μm) were stained with haematoxylin and eosin. The slides were assigned a nerve injury score, as described previously, by a neuropathologist who was blinded to the experimental groups.

**Statistics**

To determine the withdrawal thresholds, we selected a sample size of at least 6, assuming a minimal meaningful difference of 7% and a within-group standard deviation (so) of 4%, based on previous studies. For other studies including paralysis and histopathology examination, the sample size was 3–4 for each group. The statistical analysis was conducted using SigmaPlot 12 (Systat Software Inc., CA, USA). The statistical significance of differences among parametric data was evaluated using a one-way analysis of variance (ANOVA) or two-way ANOVA. When significant differences were observed, the Student–Newman–Keuls post hoc tests were performed for between-group comparisons and comparisons at each time point. The statistical significance of differences among non-parametric data was evaluated using a Kruskal–Wallis test. A value of P<0.05 was considered statistically significant.

**Results**

**Characterization of SRLPs**

The microstructure and particle size of SRLP-10 and SRLP-25 observed using SD are shown in Figure 1A and B. SRLP-10 appeared as polygon-shaped fragments or angular particles, whereas SRLP-25 appeared as sphere shapes or round polygonal fragments. The average values of the longest diameters of SRLP-10 and SRLP-25 were 14.3 μm (range 2.8–199 μm) and 12.3 μm (range 2.2–181 μm), respectively. The distribution of the longest diameters is shown in Figure 1C.
SRLP-10 was stable in a powdery state at room temperature, whereas SRLP-25 tended to become massed together at room temperature; therefore, SRLP-25 was cooled with ice until injection. SRLP-10 and SRLP-25 were both well dispersed in normal saline with the surfactant (Tween 80).

**Lidocaine content**

The mean (so) lidocaine content was 7.49 (0.15)% (w/w) for SRLP-10 and 24.4 (1.3)% (w/w) for SRLP-25.

**In vitro lidocaine-release rate study**

The in vitro lidocaine-release profiles of SRLP-10 and SRLP-25 are shown in Figure 2. The total (i.e. 100%) lidocaine content was calculated from the actual lidocaine content in the SRLPs as determined above. The SRLP-10 released 19.1% (w/w) of the loaded lidocaine within 1 h, 46.9% within 6 h, 68.5% within 1 day, 82.6% within 3 days, and 95.9% within 7 days. Approximately 1.4% of the lidocaine remained in the SRLP-10 after 2 weeks. The SRLP-25 released ~25.6% (w/w) of the loaded lidocaine within 1 h, 46.7% within 6 h, 59.5% within 1 day, 72.0% within 3 days, and 73.0% within 7 days. Even after 2 weeks, 20% of the loaded lidocaine was not released.

**Effect on hypersensitivity in the postoperative pain model**

The paw incision immediately induced mechanical hypersensitivity in the rats, as indicated by the reduced paw withdrawal threshold (Figs 3 and 4). Mechanical hypersensitivity was observed 30 min after the paw incision when compared with pre-surgical values in the control group (PLA-treated group).

Epidural administration with SRLP-10 (80 mg) produced an anti-hypersensitivity after paw incision \( F(3,20)=38.328, P<0.001 \) by two-way ANOVA; Fig. 3). In the group treated with SRLP-10 (80 mg), the withdrawal thresholds were significantly higher than in the other three groups \( P<0.001 \) by the Student–Neuman–Keuls post hoc test. Significant
differences were observed from 30 min after injection up to 7 days when compared with the control group (\(P<0.05\) by the Student–Neuman–Keuls post hoc test). Treatment with SRLP-10 (40 mg) did not produce anti-hypersensitivity. The groups treated with SRLP-25 (40 and 60 mg) showed anti-hypersensitivity [\(F(3,20)=15.287, P<0.001\) by two-way ANOVA; Fig. 4]. The group treated with SRLP-25 (60 mg), the withdrawal thresholds were significantly higher than those

---

**Fig 2** The cumulative release of lidocaine from SRLPs in PBS was calculated. The percentage of lidocaine released from the SRLPs with regard to the actual lidocaine content in the SRLPs is shown as mean (SD) (\(n=4\)).

**Fig 3** Withdrawal thresholds after the epidural injection of SRLP-10 (40 and 80 mg) in rats with paw incision determined with the von Frey test. The threshold of the group treated with SRLP-10 (80 mg) was higher than that of the control group (by two-way ANOVA with the Student–Neuman–Keuls post hoc test). The group treated with SRLP-10 (80 mg) showed anti-hypersensitivity for 7 days after the epidural injection. The threshold of the group treated with SRLP-10 (40 mg) was not different from that of the control group. Lidocaine (2 mg) only produced anti-hypersensitivity at 30 min after epidural injection. Data are shown as mean (SD) (\(n=6\) each group). \#\#\#\# \(P<0.05\) compared with the control group.
of the control group (P<0.001 by the Student–Neuman–Keuls post hoc test) and lidocaine (2 mg)-treated group (P<0.007 by the Student–Neuman–Keuls post hoc test). Significant differences were observed from 30 min after injection up to 7 days when compared with the control group (P<0.05 by the Student–Neuman–Keuls post hoc test). In the group treated with SRLP-25 (40 mg), the withdrawal thresholds were significantly higher than in the control group (P<0.001 by the Student–Neuman–Keuls post hoc test). There was no difference in withdrawal thresholds between the groups treated with SRLP-10 (80 mg) and SRLP-25 (60 mg) (P=0.822 by two-way ANOVA, data not shown).

Epidural injection of lidocaine (2 mg) produced anti-hypersensitivity and the withdrawal threshold was significantly higher at 30 min after injection when compared with the control group (P<0.05 by the Student–Neuman–Keuls post hoc test after two-way ANOVA). The effect had disappeared by 2 h after the injection, and the paw withdrawal thresholds were not different from those of the control group thereafter.

Paralysis
To determine the motor effects after the epidural injection of SRLPs, we evaluated the paralysis score and rota-rod latencies for rats without paw incision. The group treated with SRLP-10 (80 mg) showed a slight motor weakness after the epidural injection (Fig. 5A). They showed a normal gait with weak hypotonia in their legs only at 15 min after injection. No hypotonia was subsequently observed, and the hypotonia was not statistically significant at any time point (by the Kruskal–Wallis test). The group treated with SRLP-25 (40 mg) showed total leg paralysis immediately after the injection and required ~75 min to recover to the pre-injection value; they also showed higher paralysis score from 15 to 30 min compared with the control group (P<0.05 by the Kruskal–Wallis test). The group treated with lidocaine (2 mg) showed total leg paralysis 15 min after the epidural injection (P<0.05 by the Kruskal–Wallis test). No effect was observed thereafter at all during the 7-day experimental period.

In the rota-rod test, the mean (sd) baseline latency was 145.1 (7.7) s (n=16), and there was no difference between groups. The rota-rod test revealed a transient impairment of motor coordination in the groups treated with SRLP-25 (40 mg) and lidocaine (2 mg) (Fig. 5B). The group treated with SRLP-25 (40 mg) showed a reduction in the latency 15 min after the epidural injection compared with the control group (P<0.05 by one-way ANOVA). The latency was also reduced at 15 min after epidural injection with 2 mg lidocaine because of total leg paralysis (P<0.05 by one-way ANOVA). The group treated with SRLP-10 (80 mg) showed no change in the rota-rod latency after the epidural injection. No effect was observed thereafter at all during the 7-day experimental period.

Effect on sensation in rats without paw incision
To determine the sensory effects of the epidural injection of SRLPs and back surgery, we performed the von Frey test and the pinprick test on rats without paw incision; the results in
the rats with sham surgery (rats with back surgery without injection of SRLP) were not different from those of the intact rats ($P=0.057$ and 0.322, respectively, by two-way ANOVA and the Kruskal–Wallis test; Fig. 6A and B). The epidural injection of SRLP-10 (80 mg) in rats without paw incision produced increased paw withdrawal thresholds in the von Frey test compared with the sham surgery group ($P<0.05$ by two-way ANOVA; Fig. 6A). The score of the pinprick test also increased in the group treated with SRLP-10 compared with the sham surgery group ($P<0.05$ by two-way ANOVA; Fig. 6A).

**Histopathology**

The spinal cord, cauda equina, dura mater, origin of the peripheral nerve, and SRLP were examined (Fig. 7). In the groups
treated with SRLP-10 (80 mg) and SRLP-25 (60 mg), no inflammation or other pathological changes were observed at any location 1 or 4 weeks after injection (n=3 each group). A reaction resembling a foreign body reaction was present around the SRLPs at 1 week (Fig. 7A and B) and 4 weeks after injection (data not shown). The infiltrating cells were mainly macrophages, including giant cells of the foreign body type. Plasma cells and other lymphocytes were also observed. In the control group, a foreign body reaction to PLA was also observed at both time points (Fig. 7C). In the group treated with lidocaine (2 mg), no inflammation of the spinal cord or other tissues was observed (Fig. 7D). Although scar tissue was observed in a small area at the injection site, we could not detect the SRLPs at 3 months after injection (n=3). Scar tissue was also observed 5 months after the injection of PLA (n=3, data not shown).

**Discussion**

The aim of this study was to evaluate the analgesic effect of epidurally injected SRLPs in a rat model of postoperative pain. In vitro, SRLP-10 and SRLP-25 showed continuous lidocaine release for 7 and 3 days, respectively. SRLP-10 injected into the epidural space inhibited hypersensitivity in rats with paw incisions for 7 days without motor paralysis. In this rat postoperative pain model, strong hypersensitivity is observed 2–3 days after paw incision. Clinical reports also suggest that severe acute postoperative pain continues for about...
3 days after surgery. Therefore, aggressive pain management during the first few days after surgery might be necessary to reduce acute postoperative pain. Thus, the duration of lidocaine release from SRLP-10 and its effect might be sufficient to manage acute postoperative pain.

In the present study, the epidural injection of SRLP-25 (40 and 60 mg) also produced anti-hypersensitivity after the paw incision. Although the paw withdrawal thresholds of the group treated with SRLP-10 (80 mg) was not statistically different from that of the group treated with SRLP-25 (60 mg) during the experimental period, the group treated with SRLP-10 (80 mg) did not show severe motor weakness. In contrast, SRLP-25 produced severe hindpaw paralysis, even in the 40 mg group. These findings suggest that the dose of lidocaine released from SRLP-10 (80 mg) can provide sensory nerve block without motor deficiency. In the rats without paw incision, noxious sensation as measured by the pinprick test was partially blocked by the epidural injection of SRLP-10 (80 mg). Therefore, this treatment produces not only anti-hypersensitivity in rats with paw incision but also anti-nociception in normal animals.

In vitro examination revealed that SRLP-10 and SRLP-25 released 19.1% and 24.6% of the loaded lidocaine, respectively, during the first hour after epidural administration. Therefore, in the rats injected with SRLP-10 (80 mg), ~1.1 mg lidocaine was gradually released into the epidural space for 1 h after the injection. In the same manner, 3.6 and 2.5 mg lidocaine were released from SRLP-25 (60 mg) and SRLP-25 (40 mg), respectively. Taken together with the paralysis scores in the group treated with 2 mg lidocaine, which showed complete motor paralysis 15 min after administration, these findings indicate that the controlled dosing of lidocaine via sustained release can provide analgesic effects without side effects such as motor dysfunction.

Although severe motor weakness of the hindpaws was observed after the epidural injection of SRLP-25, other obvious behaviours that might be related to an overdose of local anaesthetics were not observed. A previous study reported that epidural lidocaine induces a dose- and time-dependent neurological injury in rats, possibly via severe nerve oedema or demyelination. In the present study, the pathological changes in the spinal cord and cauda equina observed near the injection site in the groups treated with SRLPs were similar to those observed in the group treated with lidocaine (2 mg) at 1 and 4 weeks after injection. Nerve inflammation, demyelination, and oedema were not observed in either group. Kirihara and colleagues reported that the epidural injection of lidocaine causes less neurological changes than intrathecal injection. Although the precise concentrations of lidocaine released from the SRLPs into the epidural and intrathecal spaces are difficult to extrapolate from our in vitro concentration measurement, the lidocaine concentration in the intrathecal space after epidural injection might be lower than the dose that induces neurological injury. In the present study, we used a light microscope but more specialized axonal imaging with
high-powered light microscopy or electron microscopy may reveal evidence of neurotoxicity.\textsuperscript{36}

In a previous study that used PLA for the sustained release of bupivacaine,\textsuperscript{12} the PLA itself did not produce nerve inflammation or demyelination. Another study reported that a foreign body reaction occurred around PLA microspheres and suggested that this reaction may cause local acidosis, which may alter the efficacy of the drug by altering its membrane-penetrating properties.\textsuperscript{18} In our study, inflammation was not observed in the spinal cord or cauda equine, although a foreign body reaction around the SRLPs and PLA was observed. It is possible that this reaction affects the anti-hypersensitivity provided by the epidurally administered SRLPs.

To our knowledge, epidural injection of analgesic agents has not been reported in a rat model of postoperative pain. In humans, however, epidural injection or infusion is widely used for postoperative pain management and reduces postoperative complications.\textsuperscript{7} Although the evaluation of spontaneous pain was not possible with the method used in the present study, our results suggest that a single epidural injection with sustained-release local anaesthetics may provide adequate analgesia for acute postoperative pain. Catheter insertion itself has the potential to cause bleeding, tissue or nerve injury, inflammation, and infection. Such complications are rare but can result in significant morbidity and mortality if the diagnosis is delayed.\textsuperscript{37} In the future, further studies should evaluate whether single epidural injections with sustained-release local anaesthetics reduce the risk of complications with an epidural indwelling catheter.

In summary, we examined the anti-hypersensitivity provided by the epidural injection of sustained-release lidocaine in a rat model of postoperative pain. SRLP-10 reduced the hypersensitivity caused by a paw incision for 7 days without inducing motor paralysis or obvious nerve injury. This technique may not only reduce postoperative pain but also reduce the risk of side effects produced by local anaesthetics administered at high concentration.

**Declaration of interest**

None declared.

**Funding**

This work was supported by Grants-in-Aid for Scientific Research (grant numbers 20591823 to H.O., 20791065 to M.T., and 20390411 to S.S.) from the Ministry of Education, Culture, Sport, Science, and Technology of Japan (Tokyo, Japan).

**References**


37 Cameron CM, Scott DA, McDonald WM, Davies MJ. A review of neuraxial epidural morbidity: experience of more than 8,000 cases at a single teaching hospital. *Anesthesiology* 2007; **106**: 997–1002