Comparison of Pre- versus Post-incision Administration of Intrathecal Bupivacaine and Intrathecal Morphine in a Rat Model of Postoperative Pain

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Background: Preclinical studies in experimental animals suggest that preemptive analgesia may improve postoperative pain management. The beneficial effects of preemptive analgesia appear less remarkable clinically. The purpose of this study is to examine the effect of pre- and post-incision administration of intrathecal bupivacaine and intrathecal morphine in a rat model for postoperative pain.

Methods: Rats with intrathecal catheters were anesthetized with halothane, and the surgical field was prepared. A saline vehicle or the test drug was administered 15 min before an incision was made in the plantar aspect of the hindpaw or after the incision was completed. After recovery, mechanical hyperalgesia to punctate and nonpunctate stimuli was measured. Rats were tested on the day of surgery for the first 5 h and each day for 6 days.

Results: In saline vehicle-treated rats, the median withdrawal threshold decreased from 522 mN to 54 mN or less, and the response frequency to pressure from application of the plastic disc increased from 0 ± 0% to 96 ± 12% or greater after incision. Hyperalgesia was persistent through 2 days after surgery and then gradually returned toward preincision values over the next 4 days. Pre- or postincision administration of either intrathecal morphine or intrathecal bupivacaine reduced hyperalgesia on the day of surgery; at all subsequent times, there were no differences between the saline vehicle groups and the drug treatment groups. There were never any significant differences between pre- and postincision treatments.

Conclusions: Early reduction in pain behaviors either by pre- or postincision management had no impact on subsequent measures of hyperalgesia in this model. These results agree with a number of clinical studies and suggest that incisional pain may be initiated and maintained differently than pain in other models. (Key words: incision, mechanical hyperalgesia, plasticity, preemptive analgesia, spinal cord.)

MANY animal studies have used preclinical models of persistent pain to investigate the effect of analgesic treatments administered before injury on the development and maintenance of subsequent pain behaviors. Greater efficacy by preinjury compared with postinjury treatments suggested that prevention of pain memory and central sensitization in the spinal cord may reduce later pain behaviors. From these experiments, it has been suggested that preemptive analgesia,¹ pain relief strategies instituted before tissue trauma, could modify the development and maintenance of postoperative pain in patients.² ³ Clinical studies on preemptive analgesia with neural blockade or opioids have been undertaken; most analyses indicate that these results are a mixture of weak positive or negative findings.⁴ ⁵

Several reasons exist for the disparity between experimental animal studies and results from clinical trials on preemptive analgesia. First, a surgical incision in humans produces tissue injury that is likely different than chemical irritation, inflammation, or nerve injury models in nonhuman animal studies. Second, the time course of persistent pain behaviors in animal models compared with pain and mechanical hyperalgesia in postoperative patients is different. Because of this lack

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of understanding of the mechanisms of pain caused by an incision, we developed and characterized a rat model for postoperative pain that is distinguished by persistent, quantifiable, mechanical hyperalgesia. Also, the time course of pain behaviors has similarities to patient’s pain after surgery, making this model ideal for preemptive analgesia studies.

If surgical incisions cause central sensitization and pain memory in the spinal cord and if this can be prevented or modified by preemptive analgesia, then intrathecally administered agents are most likely to show a positive effect in this model. The purpose of the present study was to evaluate the preemptive effects of intrathecal morphine and intrathecal bupivacaine, agents useful for postoperative patients, in this rat model for postoperative pain and compare these pain behaviors with postincision treatment and with an untreated control group. Preliminary reports of these data have been made.7,8

Methods and Materials

General

These experiments were reviewed and approved by the Institution’s Animal Care and Use Committee. The animals were treated according to the Ethical Guidelines for Investigations of Experimental Pain in Conscious Animals as issued by the International Association for the Study of Pain.9

Experiments were performed on adult (weight, 300–350 g), male Sprague-Dawley rats (Harlan, Indianapolis, IN) housed in pairs before surgery; food and water were available ad libitum. Postoperatively, the animals were housed individually with sterile bedding consisting of organic cellulose fiber (Cellu-Dri®, Shepherd Specialty Papers, Inc., Kalamazoo, MI). The incisions were checked daily, and any sign of wound infection or dehiscence excluded the animal from the study. At the end of the protocol, all animals were killed with an overdose of a mixture of pentobarbital and phenytoin.

Intrathecal Catheter Placement

For subarachnoid administration of morphine, intrathecal catheters were placed in rats anesthetized by an intraperitoneal injection of chloral hydrate (250–300 mg/kg) and supplemented with halothane if needed. After sterile preparation of the posterior neck, a small PE-10 catheter (8.5 cm) was inserted through an opening in the atlantooccipital membrane to the lumbar spinal cord according to the method of Yaksh and Rudy.10 The wound was closed with deep followed by cutaneous interrupted sutures. After recovery, these animals were examined for any apparent motor or sensory deficits; if any were present, these animals were killed.

One day before the proposed experiments, rats were injected intrathecally with 20 μl of 2% lidocaine, flushed with 10 μl of saline, and observed for bilateral hindlimb paresis; if bilateral paresis did not occur, the rat was excluded from the study. The intrathecal catheters were flushed with saline again, and experiments were begun not less than 4 days after placement.

Preliminary studies using intrathecal bupivacaine showed that greater injection volumes caused respiratory depression and forelimb weakness, probably from cephalad migration of bupivacaine injected through 8.5 cm intrathecal catheters. Placement of an 11-cm intrathecal catheter minimized the cephalad spread of the bupivacaine; therefore, rats for intrathecal bupivacaine injection had an 11-cm catheter placed in the same manner as the 8.5-cm intrathecal catheters. After 3 days recovery, the 11-cm intrathecal catheter was tested with 20 μl of 2% lidocaine (flushed with 10 μl of saline) for motor and sensory block. Commonly, there was preferential motor block to one side. This side was then tested for sensory blockade; pinprick and pinch with a blunt forceps were used as noxious stimuli, and absence of vocalization and escape behavior with the upper extremities indicated sensory blockade. The intrathecal catheter was again flushed with saline, and the rats were returned to the animal care unit for 48 h to recover. The side with a negative response to the pinprick and pinch was designated to receive the incision.

Foot Incision

All rats were anesthetized with 1.5–2% halothane delivered via a nose cone and administered an intramuscular injection of penicillin, 30,000 U, in the triceps muscle. As described previously,11 the plantar aspect of either hindpaw was prepared in a sterile manner with a 10% povidone-iodine solution and draped. A 1-cm longitudinal incision was made with a number 11 blade through skin and fascia of the plantar aspect of the foot, starting 0.5 cm from the proximal edge of the heel and extending toward the toes. The plantaris muscle was elevated and incised longitudinally, and the muscle origin and insertion remained intact. After hemostasis with gentle pressure, the skin was apposed with two mattress sutures of 50 nylon on an FS2 needle (fig. 1A), and the wound site was covered with a mixture of polymixin B, neomycin, and bacitracin oint-
Fig. 1. Effect of intrathecal morphine administered before (preincision) or after (postincision) foot incision on punctate mechanical hyperalgesia from 1 h to 6 days later. The results are expressed as raw withdrawal threshold versus time data. Each line represents one rat. The withdrawal thresholds are on a log scale. (A) Diagram of the plantar aspect of the rat foot showing site of application of von Frey filament (small circle) and site of application of plastic disc (larger, darkened circle). (B) Withdrawal thresholds after incision in saline-treated rats. (C) Withdrawal thresholds of rats administered 5 μg of intrathecal morphine 15 min before incision. (D) Withdrawal thresholds of rats administered 5 μg of intrathecal morphine after incision. Pre = time before foot incision. MS = morphine sulfate. †P < 0.05 versus pre by Friedman and Dunnett’s test. ††P < 0.05 versus saline by Kruskal-Wallis and Dunn’s test.

After surgery, the animals were allowed to recover in their cages.

Behavioral Testing

On the day of the experiment, the rats were placed individually on an elevated plastic mesh floor covered with a clear plastic cage top (21 × 27 × 15 cm) and allowed to acclimate. Baseline pain behaviors before foot incision were measured as will be described.

Semmes-Winston von Frey filaments (Stoelting, Wood Dale, IL), flexible nylon filaments attached to a plastic handle, were calibrated by measuring the force in milli-Newton (mN) required to bend the filaments when pressed against a hard surface. As the filament’s diameter (thickness) increases, the force required to bend the filament is greater. Withdrawal responses to punctate stimulation were determined using these von Frey filaments applied to an area adjacent to the intended

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wound (fig. 1A) from underneath the cage through openings (12 × 12 mm) in the plastic mesh floor as described previously.8 Each von Frey filament was applied once until the filament bent, starting with 15 mN and continuing until a withdrawal response occurred or 522 mN (the cut-off value) was reached. This was repeated three times with a 5- to 10-min test-free period between withdrawal responses. The lowest force from the three tests producing a response was considered the withdrawal threshold. The cut-off value, 522 mN, was recorded even if there was no withdrawal response to this force.

To assess responses to a nonpunctate mechanical stimulus, a 5-mm clear plastic disc attached to a von Frey filament (bending force, 400 mN) was applied directly on the intended incision site (fig. 1A) from underneath the cage through openings in the plastic mesh floor. A positive response to the nonpunctate stimulus was defined as a withdrawal response (linch) or when the foot was lifted off of the mesh floor by the plastic disc. This test was repeated three times with approximately 3-5 min between measurements; from these three trials, the response frequency was calculated.

Pinprick was performed once each test period. A 5-mm long tip of a safety pin attached to a von Frey filament (bending force, 600 mN) was applied between the distal pads of the foot, and the average withdrawal frequency was calculated from the single test. The pinprick test estimated the duration of analgesia to a supra-maximal noxious stimulus produced by the spinally administered test drug and enabled comparison with the time course of inhibition of hyperalgesia.

**Experimental Protocols**

In a previous study, we demonstrated that intrathecal morphine produced dose-dependent inhibition of mechanical hyperalgesia in this rat model.11 The onset of morphine-induced hypoalgesia occurred within 10 min and lasted approximately 2-3 h; the maximum effect was produced by intrathecal injection of 5 μg. In the present study, baseline pain behaviors were measured, and rats were randomized to receive saline vehicle before foot incision, 5 μg of intrathecal morphine 15 min before incision, or 5 μg of intrathecal morphine injected after the wound was closed but before halothane was discontinued. Surgical time was approximately 15 min. Responses to von Frey filaments, the plastic disc, and pinprick were measured 1, 3, 4, and 5 h after incision and daily for the next 6 days by a person unaware of the drug administered.

Previous animal studies by others indicate that doses greater than 5 μg of intrathecal morphine may prevent the development of persistent pain.12,13 Therefore, baseline pain behaviors were measured in 24 additional rats that were randomized to receive saline vehicle before foot incision, 30 μg of intrathecal morphine 15 min before incision, or 30 μg of intrathecal morphine injected after the wound was closed but before the anesthetic was discontinued. Pain behaviors were measured 1, 3, 4, and 5 h after incision and daily for the next 6 days by a person unaware of the drug administered.

In preliminary studies, we were able to obtain a more consistent, dense spinal analgesia with 20 μl of 1% bupivacaine than we were able to observe with lower concentrations and with this volume avoided cephalad spread, respiratory compromise, and forelimb weakness. For studies of the effect of intrathecal bupivacaine on the development of incisional pain, 24 rats were pretested for baseline pain behaviors and randomly assigned to one of three groups. Those in the preincision treatment group were anesthetized with halothane and then given an intrathecal bolus of 20 μl of 1% bupivacaine, followed by an infusion of 1% bupivacaine at a rate of 75 μl/h for 1 h. Fifteen minutes after the bolus injection, the hindpaw preferentially blocked by the intrathecal injection of 20 μl of 2% lidocaine administered 1 day earlier was incised. After the closure of the incision, the rat was placed on the plastic mesh and allowed to recover. The rats assigned to the postincision treatment group were anesthetized with halothane followed by the hindpaw incision on the designated foot. On completion of the surgery, a bolus of 20 μl of 1% bupivacaine was injected via the intrathecal catheter followed immediately by an infusion of 75 μl of 1% bupivacaine infused at 75 μl/h for 1 h. Rats in the saline vehicle group were injected with 20 μl of saline before foot incision and administered an infusion of 75 μl/h for 1 h. The rats were tested 30 min to 1 h after surgery for pinprick and pinch with a forceps; motor block was present, and lack of vocalization and escape behavior indicated sensory anesthesia. Pain behaviors were measured 2, 3, 4, and 5 h after incision and daily for the next 6 days by a person unaware of the drug administered. Sutures were removed at the end of postoperative day 2 in all animals.

**Drugs**

Preservative-free morphine sulfate (1 μg/μl) was purchased from Abbott Laboratories (Chicago, IL); the dose administered was based on micrograms of morphine.
sulfate. Bupivacaine HCl was purchased from Sigma (St. Louis, MO), dissolved in preservative-free saline, and administered as 1% bupivacaine HCl. All drugs administered intrathecally were flushed with 10 μl of preservative-free saline.

Statistical Analyses
Data are presented as the median or the mean ± SD where appropriate. Data were compared using nonparametric analyses. Friedman’s test for within group and the Kruskal-Wallis test for among group comparisons were used. Multiple comparisons after Friedman’s test were performed using Dunnett’s test to determine if the response measured after incision was different than the response before incision. Because the response before incision was already at cut-off and could not be greater, a one-tailed test was used. Multiple comparisons after the Kruskal-Wallis test were performed using a two-tailed Dunn’s test; P < 0.05 was considered significant.

Results

**Intrathecal Morphine (5 μg)**
In the saline-treated group (fig. 1B), the median withdrawal threshold decreased from 522 mN before surgery (pre) to 39 mN 1 h after foot incision and remained less than 34 mN throughout the day of surgery (P < 0.05 vs. pre). On postoperative day 1 through day 6, the median withdrawal thresholds gradually increased. In the group treated with 5 μg of intrathecal morphine before foot incision (fig. 1C), the withdrawal thresholds were significantly higher compared with pretreatment with saline vehicle at 1 and 3 h (P < 0.05 vs. saline). Otherwise, there were no significant differences between these groups. Similarly, when 5 μg of intrathecal morphine was administered after foot incision, withdrawal thresholds again did not decrease immediately after surgery (fig. 1D) and were significantly higher than the saline-treated group (P < 0.05 vs. saline) at 1 and 3 h only. There were no differences between morphine-treated groups and the saline vehicle control group 4 h after surgery through postoperative day 6; further, there were never any significant differences in withdrawal thresholds between pre- and postincision treatments with 5 μg of intrathecal morphine.

For the nonpunctate stimulus, the response frequency increased from 0 ± 0% before incision to 96 ± 12% or greater 1–5 h after the plantar incision (fig. 2A); the responses gradually declined during postoperative days 2–6. Except for decreased frequencies at 1 h and 3 h after foot incision (P < 0.05 vs. saline), preincision treatment with 5 μg of intrathecal morphine was not different than saline. In the group treated with 5 μg after foot incision, the response frequencies at 1 and 3 h were again initially decreased (P < 0.05 vs. saline); thereafter, no differences were present compared with the saline vehicle treatment.

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Fig. 2. (A) Effect of intrathecal morphine administered before or after incision on nonpunctate mechanical hyperalgesia from 1 h to 6 days later. (B) Withdrawal frequency to pinprick. The results are expressed as the mean ± SD. Pre = time before foot incision. MS = morphine sulfate. *P < 0.05 versus pre by Friedman and Dunn's test. † P < 0.05 versus saline by Kruskal-Wallis and Dunn's test.
There were no differences in responses to the nonpunctate stimulus in groups administered 5 μg of intrathecal morphine before or after surgery throughout the study. The withdrawal frequency to pinprick was reduced 1 h after foot surgery in both groups treated with intrathecal morphine (fig. 2B); therefore, analgesia to pinprick was short-lived, and inhibition of hyperalgesia was present for slightly longer.

Intrathecal Morphine (30 μg)
In a different vehicle-treated group (fig. 3A), persistent punctate hyperalgesia after foot incision was observed followed by a return toward priccision thresholds. Administration of 30 μg of intrathecal morphine before foot incision (fig. 3B) caused a greater withdrawal threshold compared with saline from 1 h to 4 h after incision (P < 0.05 vs. saline), but this early effect was not different than the vehicle-treated group from 5 h through 6 days. Similar results were observed when 30 μg of intrathecal morphine was administered after foot incision (fig. 3C). Overall, except for an early reduction in hyperalgesia on the day of surgery, no sustained increase in withdrawal threshold by these high doses of intrathecal morphine could be detected on subsequent days; in addition, no differences between pre- and postincision treatment were present throughout the study. The response frequency to the nonpunctate stimulus was significantly decreased compared with saline for the first 4 h (P < 0.05 vs. saline) in rats pretreated with 30 μg of intrathecal morphine (fig. 4A). Similarly, administration of 30 μg of intrathecal morphine after incision inhibited responses to the nonpunctate stimulus during the first day (P < 0.05 vs. saline) only. No greater reduction in hyperalgesia was produced by pretreatment compared with posttreatment with 30 μg of intrathecal morphine. The withdrawal frequency to pinprick was decreased for 1–3 h in rats treated with 30 μg of intrathecal morphine, a slightly shorter duration than inhibition of hyperalgesia (fig. 4B).

Intrathecal Bupivacaine
In the group of rats administered intrathecal bupivacaine before foot incision, only the withdrawal threshold at 2 h was significantly greater (P < 0.05 vs. saline) than the saline vehicle-treated group (fig. 5A–C). When intrathecal bupivacaine was administered after foot incision, again the withdrawal threshold was only different from saline 2 h after foot incision (P < 0.05). No other differences between treatment and vehicle groups were evident. There were no differences in withdrawal thresholds between pre- and postincision bupivacaine treatments throughout the study period.

In rats pretreated with intrathecal bupivacaine, the response frequency to the nonpunctate stimulus was decreased (P < 0.05 vs. saline) 2 h after incision and then subsequently increased to the same level as the vehicle-treated rats (fig. 6A). There were never any differences between the pre- and postincision treatment groups throughout the experiment. All groups recovered motor function by 2 h after surgery. Although inhibition of hyperalgesia was apparent at 2 h, the withdrawal response to pinprick was intact by this time (fig. 6B).

Discussion
This is the first study in experimental animals to use an incision as the injury causing persistent pain to test the preemptive analgesia hypothesis and its relation to human postoperative pain. No significant differences between preincision and postincision administration of intrathecal morphine or intrathecal bupivacaine on mechanical hyperalgesia in this rat model of postoperative pain were observed. Withdrawal thresholds and response frequencies were significantly altered only during the acute, initial effect of the drug, i.e., within the first 3–5 h of testing. One to 6 days after surgery, when a reduction in hyperalgesia would be expected if preemptive analgesia was effective, no significant difference could be detected between the pre- and posttreatment groups. Importantly, after the early initial effect of drug had dissipated, differences could not be demonstrated between the treatment groups and those rats administered intrathecal saline vehicle; therefore, prevention of early pain behaviors either by pre- or postincision treatment had no long-lasting impact on subsequent measures of hyperalgesia in this model.

A number of investigators have examined preemptive analgesia with systemically administered opioids in postoperative patients. Some initial studies suggested that early administration of intravenous morphine was advantageous in patients undergoing abdominal hysterectomy, subsequent studies showed minimal benefit. If pain memory in the dorsal horn of the spinal cord during and after surgery is as important as other animal models suggest, then preemptive analgesia using intrathecal local anesthetics or intrathecal opioids should have modified the maintenance of hyperalgesia in this model.

Neuraxial Opioids: Clinical and Preclinical Studies
Beneficial effects of pretreatment with intrathecal morphine have been shown by others in some animal
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![Graphs showing the effect of saline and morphine on withdrawal threshold](image)

Fig. 3. Effect of 30 μg of intrathecal morphine administered before or after surgery on punctate mechanical hyperalgesia from 1 h to 6 days later. The results are expressed as raw withdrawal threshold versus time data with each line representing one rat. (A) Withdrawal thresholds after incision in saline-treated rats. (B and C) Withdrawal thresholds after incision in rats administered 30 μg of intrathecal morphine before and after incision, respectively. Pre = time before foot incision. MS = morphine sulfate. *P < 0.05 versus 0 min by Friedman and Dunn’s test. †P < 0.05 versus saline by Kruskal-Wallis and Dunn’s test.

models of persistent pain. High doses (30 μg) of intrathecal morphine attenuated formalin-induced, late pain behaviors, even after reversal of morphine by naloxone. Similar doses, administered preemptively, reduced autotomy and spinal cord hyperexcitability after sciatic nerve ligation. In the present study, pretreatment with a low dose of intrathecal morphine (5 μg) produced inhibition of mechanical hyperalgesia early, but this did not persist beyond the expected duration of the drug effect. Because others have reported remarkable responses with greater doses of intrathecal morphine (30–50 μg) in rat models, the 30-μg dose was studied, and again no long-lasting effect was observed.

Few clinical studies on preemptive analgesia with administration of only neuraxial opioids have been performed. Katz et al. reported that lumbar epidural fentanyl reduced visual analog scale (VAS) pain scores and produced transient reduction of morphine use in patients undergoing thoracotomy. Other studies have examined the preemptive effect of epidural local anesthetic and opioid combinations and have observed no differences between pre- and posttreatments.

Neuraxial Local Anesthetics: Clinical and Preclinical Studies
The preemptive analgesia hypothesis for intrathecal local anesthetics was initiated by experiments in animals using a hindpaw injection of formalin—a brief,
Fig. 4. (A) Effect of intrathecal morphine (30 µg) administered before or after incision on nonpunctate mechanical hyperalgesia from 1 h to 6 days later. (B) Withdrawal frequency to pinprick. The results are expressed as the mean ± SD. Pre = time before foot incision. MS = morphine sulfate. *P < 0.05 versus 0 min by Friedman and Dunn’s test. †P < 0.05 versus saline by Kruskal-Wallis and Dunn’s test.

intense chemical irritation. Pretreatment with intrathecal lidocaine before formalin injection was more effective than postformalin treatment for preventing ‘late’ pain behaviors (10–60 min after injection) and suggested that nociceptive input during the first 10 min after formalin injection caused central nervous system plasticity that magnified late pain behaviors. Subsequent studies apparently confirmed this. No studies in other animal models have provided strong data supporting preemptive analgesia with intrathecal local anesthetics for preventing persistent pain behaviors.

Early clinical studies suggest that spinal blockade of nociceptive inputs during surgery may prevent mechanical hyperalgesia for several days after herniorrhaphy. From this early positive result, epidurally administered local anesthetics have been used to produce preemptive analgesia for postoperative pain in patients applying study designs recommended by Mcquay. Katz et al. reported that a single preemptive dose of epidural bupivacaine (0.5%) reduced pain rating by pain questionnaire but not by VAS after lower abdominal surgery. A short-lived (12–24 h) reduction in morphine consumption was also noted. In contrast to this one partially positive study, preemptive epidural bupivacaine did not have any greater beneficial effect than postincision injection in patients undergoing thoracotomy, lower abdominal surgery, or abdominal hysterectomy. No difference was observed in children undergoing hernia repair or circumcision either.

Critical reviews of these clinical studies suggest that the concentration of bupivacaine administered epidurally for most postoperative patients is not sufficient to block all afferent input from the surgical stimulus, therefore, incomplete blockade of input during tissue injury potentially obscures the positive results. Perhaps in future clinical studies, more complete neural blockade will produce long-term beneficial effects.

In the present study, intrathecal administration of 1% bupivacaine was used. This dose and concentration produced flaccid paralysis of the incised foot and prevented pain behaviors caused by noxious pinch with a forceps. Although it is not assured all afferent input is blocked by this treatment, the degree of blockade is likely greater than that achieved in clinical studies with epidural administration of lesser concentrations of local anesthetics; yet, no positive effect was observed.

Rat Model for Postoperative Pain
A difficulty with the interpretation of results from studies on preemptive analgesia in animal models is to relate them directly to the clinical postoperative state. There are several reasons for this. First, no models other than the one described in this study use a surgical incision as the noxious event. An incision is intense, focal tissue destruction with injury of superficial and deep structures. The mechanisms for initiation and maintenance of pain after incision likely involve a combination of nerve injury, inflammation, pH changes, and central nervous system plasticity, but it must be emphasized that the contribution
of these changes is not known. Because the etiology of incisional pain may be different than inflammatory pain, chemical irritation, or nerve injury, the responses to preemptive treatments may also differ.

Second, the onset, progression, and time course of incisional pain and pain behaviors in other models are not the same. In this model, the actual incision requires only minutes to perform, and hyperalgesia is most remarkable immediately after surgery; the pain behaviors decrease gradually over several days. The onset of pain in other animal models varies from immediately after injection of formalin$^{1,12,24}$ to hours and even days after nerve injury.$^{25}$ The progression of pain behaviors depends on the particular model. After formalin injection, pain behaviors are biphasic; in others, pain behaviors are greatest several days after injury.$^{24}$ Further, the time course in other animal models of persistent pain may occur over minutes as in formalin$^{1,12}$ or capsaicin$^{23}$ injection or up to weeks and months as in autotomy$^{31}$ or nerve injury.$^{25}$ Therefore, the time over which pain behaviors are measured varies among models and is important in preemptive analgesia studies as noted by McQuay.$^{3}$ In postoperative patients, pain is usually the greatest immediately after surgery, is severe for several days later, and then gradually decreases. Surgical incisions do not necessarily cause chronic pain like inflammation or nerve injury. The duration of mechanical hyperalgesia in this study is similar to the period of mechanical sensitivity$^{25}$ and evoked pain from coughing$^{36}$ observed postoperatively in humans.

There are advantages to the use of this animal model

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Notes on the diagrams:

**Fig. 5.** Effect of intrathecal bupivacaine administered before or after surgery on punctate mechanical hyperalgesia from 1 h to 6 days later. The results are expressed as raw withdrawal threshold versus time data with each line representing one rat. (A) Withdrawal thresholds after incision in saline-treated rats. (B and C) Withdrawal thresholds after incision in rats administered intrathecal bupivacaine before and after incision, respectively. Pre = time before foot incision. MS = morphine sulfate. *P < 0.05 versus 0 min by Friedman and Dunnett's test. †P < 0.05 versus saline by Kruskal-Wallis and Dunn's test.
of postoperative pain to clinical studies. Clinical studies on preemptive analgesia use a particular intervention to modify two variables: pain score(s) and opioid use. Most studies result in a mixed effect of a small reduction in opioid use with the same pain scores or a reduced pain score and the same opioid requirement. In the present study, a behavioral assessment of surgical wound "mechanical sensitivity" was made, and differences among the treatment groups were not found. Also, no treatments other than halothane were administered to the animals except the study drug; therefore, no confounding analgesics or anesthetics could inadvertently preempt incisional pain.

As opposed to some clinical studies that either administer an analgesic treatment before or after surgery, an untreated (vehicle) control group was also present. A comparison between those rats treated with an analgesic intervention (either before or after surgery) and those administered vehicle should indicate whether the postincision treatment also prevented the pain behaviors. Except for the day of surgery, no differences between the vehicle-treated animals and the analgesic-treatment groups were present. This indicates that despite eliminating pain early after surgery and reducing pain during the first day, the same mechanisms maintaining postoperative pain are still present and are able to generate equivalent pain behaviors later. These data also suggest that the mechanisms for maintenance of pain from an incision are different than those mechanisms in other models in which preemptive treatments are effective.

Others propose the duration of blockade used in clinical studies is insufficient to produce a significant preemptive effect, and the blockade should be extended well into the postoperative period. For local anesthetic blockade in the present study, the infusion was extended for 1 h after surgery in both groups, a longer duration than some clinical studies, which used a single dose of epidural local anesthetic. Similarly, the effect of intrathecal morphine lasted for hours after surgery. Criteria for a rigorous preemptive trial were maintained. If preemptive treatment must be continued well into the postoperative period to produce the beneficial effect, then this is not a preemptive effect by itself.

The current study does not exclude the possibility that preemptive analgesic treatments may reduce the "stress response" during surgery better than postincision treatments or that certain chronic pain states like postamputation phantom limb pain caused by surgery may be reduced by preemptive analgesia strategies.

**Conclusion**

After early treatment of incisional pain, the surgical wound appears capable of generating pain behaviors equivalent to untreated animals; thus, early treatment strategies did not necessarily modify later hyperalgesia. Also, this indicates that maintenance of hyperalgesia after surgery is likely generated from the incision de-
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spite treatments aimed at preventing central nervous system plasticity. The marked success of preemptive treatments in other animal models of persistent pain and the mixed results seen clinically in postoperative patients and in this model suggest that the mechanisms for initiation and maintenance of pain after these other injuries may not parallel the postoperative course well. We hypothesize that phenomena such as arthritis-induced dorsal root reflexes or nerve injury-reduced dorsal horn excitotoxicity, occurring in models positive for preemptive analgesia, may not be as important in incisional pain.

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