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Effect of Preemptive Nerve Block on Inflammation and Hyperalgesia after Human Thermal Injury

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Background: **Postoperative pain relief may be improved by reducing sensitization of nociceptive pathways caused by surgical trauma. Such a reduction may depend on the timing and efficacy of analgesia and the duration of the nociceptive block *versus* the duration of the nociceptive input. We examined whether a prolonged nerve block administered before a superficial burn injury could reduce local inflammation and late hyperalgesia after recovery from the block.**

Methods: **The effects of a preemptive saphenous nerve block on primary and secondary hyperalgesia, skin erythema, and blister formation, were compared to the opposite unblocked leg for 12 h after bilateral thermal injuries (15 × 25 mm, 49°C for 5 min) in 20 healthy volunteers. Recovery from the block was identified by return of sensation to cold.**

Results: **Six subjects were excluded because of insufficient initial block (2 subjects) or because the block lasted beyond the study period (4 subjects). The remaining 14 subjects experienced significantly reduced primary ($P = 0.005$) and secondary hyperalgesia ($P = 0.01$) in the blocked leg after return of cold sensation compared to the unblocked leg. Erythema intensity and blister formation were not significantly affected by the blockade ($P = 0.94$ and $P = 0.07$, respectively).**

Conclusions: **These data suggest that a prolonged, preemptive nerve block reduced late hyperalgesia after thermal injury, whereas the erythema and blister formation were not significantly affected. (Key words: Analgesia: hyperalgesia. Nerve block: preemptive. Nerves: neurogenic inflammation; sensitization; thermal injury. Pain: postoperative.)**

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INJURY causes inflammation, which can lead to prolonged sensitization of nociceptive pathways. Primary and secondary hyperalgesia are well-established aspects of this process. Hyperalgesia describes the phenomenon of increased pain intensity in response to a normally painful stimulus.[1] Primary hyperalgesia refers to the changes in sensation within the injury, whereas secondary hyperalgesia refers to sensory changes in the undamaged tissue surrounding the injury.[2] Secondary hyperalgesia reflects central sensitization, whereas primary hyperalgesia results from either central or peripheral sensitization or a combination of the two, depending on the type of injury.[3–8] The clinical consequences of these functional changes are not clear, but it is known that these changes may reduce pain threshold, increase pain to suprathreshold stimuli, and may even lead to chronic pain. Thus, prevention of this sensitization appears to be a rational step in pain treatment. Several experimental studies have demonstrated advantages of preemptive analgesia,[9] whereas clinical evidence is less convincing.[9–11] One explanation may be that duration of the nociceptive input in most clinical studies outlasts the blockade and causes sensitization of nociceptive pathways after the block resolves.

In the current study, we investigated whether a prolonged and preemptive nerve block could reduce late hyperalgesia after recovery from nerve block and di-

minish local inflammation after thermal injury in healthy volunteers.

Methods

Subjects

We studied 20 healthy volunteers aged 22–46 yr (18 men and 2 women). Informed consent was obtained from all subjects and the study was approved by the local Ethics Committee and the Danish National Health Board.

Procedure

Baseline measurements, including assessment of skin color and mechanical pain detection threshold, were done in the middle of expected innervation areas of the saphenous nerves in both legs. After baseline measurements were taken, either the right or left leg was chosen randomly for nerve block and the saphenous nerve was blocked where it leaves the fascia. On establishment of complete block, a thermal injury was induced on each leg, starting with the unblocked leg. All measurements, that is, area with abolished cold sensation, skin erythema, blister formation, and primary and secondary hyperalgesia, were made in the mentioned order 1, 4, 6, 8, 10, and 12 h after the injuries. Experiments were performed in a quiet room with a temperature of 20–22°C and the subjects reclining. Neither the subjects nor the investigator could be blinded because of the obvious difference between the blocked and unblocked leg, so the subjects were instructed to keep their eyes closed during all measurements, which ensured that they had no knowledge of the results of the measurements. Further, the subjects were not medically knowledgeable and they were not aware of the specific purpose of the study.

Nerve Block

After baseline measurements were taken, the saphenous nerve of the right or left leg was located with external nerve stimulation (Neuromatic 2000 M, Dantec, Herlev, Denmark). The location was confirmed with invasive nerve stimulation (Stimuplex S, B. Braun, Melsungen, Germany) *via* a 22-G injection cannula. The block was induced with 9 ml lidocaine 1% without epinephrine and considered effective in the presence of anesthesia to a 52°C stimulus (1°C/s from 32°C). The area with abolished cold sensation was mapped using a gauze soaked with alcohol at the same times as the other measurements. Recovery from the block was defined by overall return of cold sensation.

Thermal Injury

Thermal injuries were produced on the medial surface of the right and left calf with a 15 × 25 mm Peltier thermode (Thermotest, Somedic A/B, Stockholm, Sweden). Induction of injury was performed in the untreated leg first followed immediately by the blocked leg. The thermode (49°C) was applied to the skin for 5 min under standardized pressure (4.5 kPa = 34 mmHg) causing first- and superficial second-degree burn injuries.[12,13] Pain intensity was rated with a verbal rank score (0–100) immediately and 2.5 min after the start of the burn stimulus. The burn caused immediate intense stinging pain, which was followed by a moderate burning pain with a more diffuse quality during the rest of the stimulation period. Spontaneous pain after the injury has not been observed in the model.

Primary Hyperalgesia

Mechanical pain detection threshold within the injured area was determined by pinprick with nine progressively rigid von Frey bristles (Somedic A/B, Stockholm, Sweden). We examined the force produced by each bristle by pressing it against a balance and measured the weight it produced when it was slightly flexed. We confirmed that the steps from 1 to 9 represent logarithmic increases in force (bristle #1 = 3 mN, 2 = 9 mN, 3 = 11 mN, 4 = 18 mN, 5 = 29 mN, 6 = 49 mN, 7 = 98 mN, 8 = 98 mN, 9 = 175 mN). Mechanical pain detection threshold was defined as the lowest force (pinprick) that produced a definite sensation of pain or discomfort. Pinprick was performed with each bristle from the thinnest, 8–10 times in the area of the injury, until some of the 8–10 stimulations were reported to be painful or unpleasant. The number of the hair producing pain was recorded and the procedure was repeated three times. The median of the three threshold measurements was reported as the mechanical pain detection threshold at that time point. If bristle #9 did not produce any pain or discomfort we assigned this observation the value 10.

Secondary Hyperalgesia

The area of mechanical hyperalgesia that developed around the burn injury was assessed with von Frey bristle #9 (175 mN). Pinprick with this bristle is in most cases a painful or unpleasant stimulus in distinct spots of the skin, although it is not universally painful. Thus,

hyperalgesia, not allodynia, was measured. Borders of hyperalgesia were determined by stimulating along eight radial linear paths arranged from the center of injury. Stimulation along each path began well outside the hyperalgesic area where slight or no pain was perceived and continued slowly toward the center of the burn injury until the subject reported a definite change in sensation, most often to a more intense pricking with a burning aftersensation. This point was marked and later traced onto a clear acetate sheet. From these eight points the area of secondary hyperalgesia was calculated using a vector algorithm.

Inflammation

To estimate the severity of inflammation, the intensity of erythema inside the injury was assessed with a handheld skin reflectance spectrophotometer (Dermaspectrometer, Cortex Technology, Hadsund, Denmark).[14,15] The spectrophotometer provided a skin erythema index based on the absorption characteristics of green and red light in the skin. Measurements were made in six spots within the burn injury. All values were recorded and the mean was calculated. The development of blisters was recorded as present or absent.

Statistics

Data were evaluated with the Sign test and Wilcoxon test for paired observations.[16] The comparisons of primary and secondary hyperalgesia in blocked *versus* unblocked leg for each subject were based on the sum of measurements obtained after return of cold sensation, divided by their number.[17] The comparison of erythema was based on area under curves for each person for the total duration of observation.[17] We present diagrams for each person, because the curves joining the medians hide important variation in shape and location of curves.[17] Blister formation at 12 h was evaluated with the Sign test. $P < 0.05$ was considered statistically significant.

Results

We studied a group of 20 subjects of which 6 subjects were excluded from comparisons of hyperalgesia, either because of insufficient block with pain during thermal injury (2 subjects) or because cold sensation did not return during the 12-h study period (4 subjects). The remaining 14 subjects had significantly reduced primary ($P = 0.005$; Wilcoxon test) and secondary hyperalgesia ($P = 0.01$; Wilcoxon test) in the blocked legs *after* return of cold sensation (recovery from block) compared to the untreated legs (fig. 1). The results are summarized in figures 2 and 3, which show the time course of the median primary and secondary hyperalgesia in the 14 subjects. Of the 18 legs with sufficient blocks, six developed blisters after 12 h, while 12 of the 18 corresponding unblocked legs developed blisters. However, this reduced incidence of blister formation in blocked legs was not statistically significant ($P = 0.07$; Sign test).

Erythema intensity was not influenced by the block ($P = 0.94$; Wilcoxon test). One of 18 subjects with effective blocks was excluded from this comparison because of skin redness caused by shaving the legs the same morning. This subject was not excluded from other comparisons because nociception apparently was not changed by the shaving and redness was identical at both sides. Results from excluded subjects (n = 6; subject number 1, 3, 5, 13, 14, and 15 in fig. 1) confirm the patterns from included subjects and demonstrate that hyperalgesia in blocked legs was reduced or equal to unblocked legs in 83 of 84 measurements.

Median pain intensity (0–100) during induction of the thermal injury was 76 at the start and 50 after 2.5 min in unblocked legs compared to 0 for both pain assessments in blocked legs. Spontaneous pain after the injury was not observed. Median duration of the nerve block according to the cold sensation test was 8 h in the study group (n = 14) and 9 h including all sufficient blocks (n = 18).

Discussion

We examined the effects of a pretraumatic nerve block on hyperalgesia, skin erythema, and blister formation after a standardized thermal injury in healthy volunteers, and compared the response to an identical injury on the unblocked leg. When the injury was performed after nerve block, primary and secondary hyperalgesia were reduced or absent after restoration of cold sensation corresponding to recovery from the block. There was a trend toward reduced blister formation 12 h postinjury in blocked legs ($P = 0.07$), but the intensity of erythema was similar with or without nerve block. The current data suggest that a preemptive nerve block reduces central hyperexcitability and possibly peripheral sensitization after recovery of cold sensation.

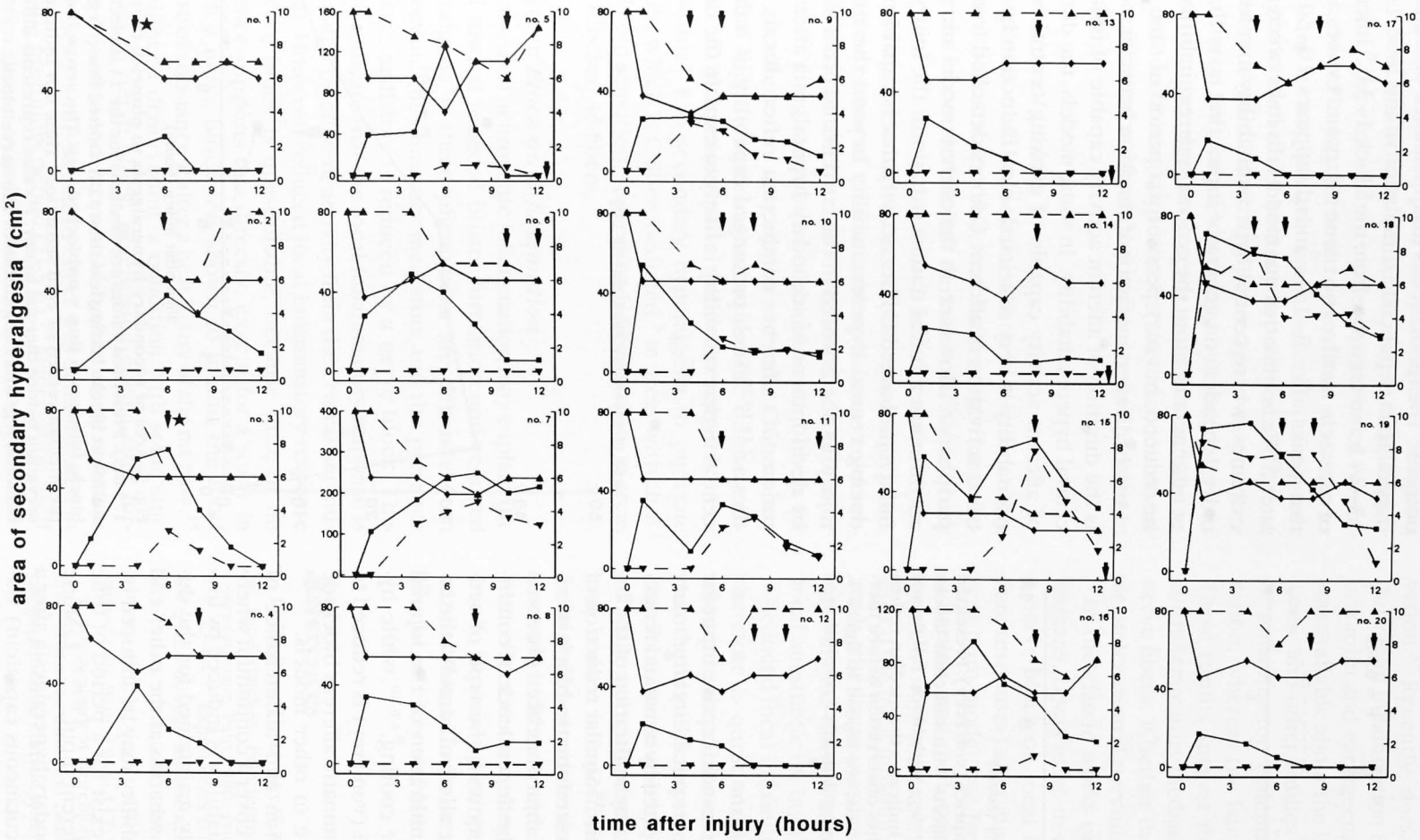

Fig. 1. Primary hyperalgesia (*right*, y-axis); *i.e.*, mechanical pain detection threshold to von Frey pinprick, in the area of the injury and secondary hyperalgesia (*left*, y-axis), *i.e.*, areas of hyperalgesia to von Frey pinprick (175 mN) outside the injuries, after thermal injury in volunteers. Dotted line = legs with nerve block; full-drawn line = unblocked legs. Primary hyperalgesia in blocked legs (▲); primary hyperalgesia in unblocked legs (♦); secondary hyperalgesia in blocked legs (▼); secondary hyperalgesia in unblocked legs (■). Arrows indicate return of cold sensation. In diagrams with two arrows, the first arrow indicates return of cold sensation in the injury and the second indicates that cold sensation has returned all over the leg. One arrow indicates that the two events occurred at the same time. The number in each diagram identifies the subject. Subjects 1 and 3 were excluded because of pain during induction of burn injury (marked with asterisk), whereas subjects 5, 13, 14, and 15 were excluded because of prolonged block. Von Frey bristle number (1–10) represents a rank scale, where 1 indicates a force of about 3 mN and 9 about 175 mN, whereas 10 indicates that 175 mN did not produce pain or discomfort. The steps from 1 to 9 are logarithmic increases in force (see Methods). Values are medians of three observations. Time 0 h indicates measurements before thermal injury. Comparison of weighted average after return of cold sensation, reveals a significant difference between primary hyperalgesia in blocked *versus* unblocked legs ($P = 0.005$; Wilcoxon test, n = 14) and significant difference in secondary hyperalgesia ($P = 0.01$; Wilcoxon test, n = 14).

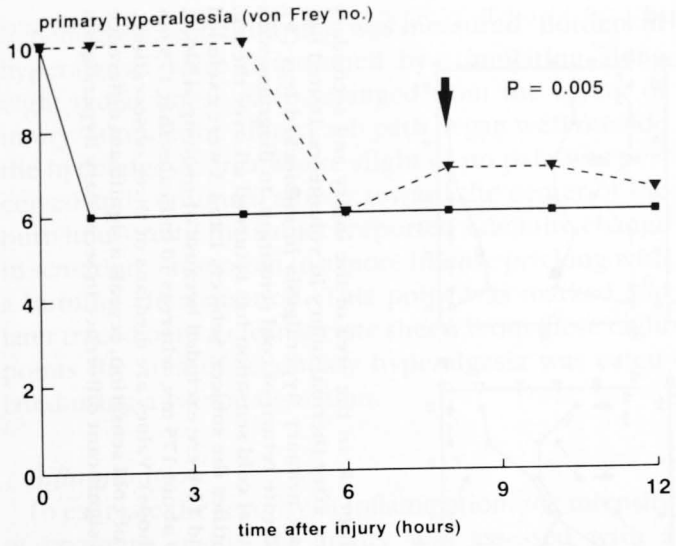

Fig. 2. Primary hyperalgesia to pinprick (von Frey). Presented values are medians for the 14 subjects with sufficient blocks lasting less than 12 h. Dotted line = legs with block; full-drawn line = unblocked legs. The arrow indicates the median return of cold sensation. Time 0 h indicates observation before thermal injury. For explanation of y-axis, see legend to figure 1. *P* value represents difference between legs after resolution of the nerve block.

Effect of Block on Hyperalgesia

The dependence of continuous nociceptive input for the maintenance of central hyperexcitability after injury in the current model, is supported by a marked reduction in secondary hyperalgesia by infiltration of the injured area with local anesthetic.[18] Similar reduction of secondary hyperalgesia by posttraumatic block of afferent activity from the site of injury has been observed in other human models.[6,19] The dependence of continuous nociceptive input differs with the type of secondary hyperesthesia, because allodynia around the injury is nearly abolished by infiltration of the injured skin with local anesthetic or cooling,[4,6,20] while hyperalgesia to punctate stimuli (von Frey) is reduced to a much lesser extent.[6] Posttraumatic afferent blockade has been found less effective in other models.[2,21–23] The mechanisms for induction and maintenance of central hyperexcitability may cover a continuum where at one end, central hyperexcitability is induced by low intensity stimulation and only maintained for the duration of the stimulus,[19,24,25] whereas at the other end of the spectrum, hyperexcitability may be induced by a brief intense stimulus and exist for a period of time apparently independent of afferent input.[6,26,27] LaMotte *et al.* demonstrated that secondary hyperalgesia after a brief intense stimulus (intracutaneous capsaicin) was prevented by a preemptive nerve block in healthy volunteers.[6] The spontaneous disappearance of secondary hyperalgesia to punctate stimulation in this model takes 13–24 h and recovery from the block 1–3 h.[6] Injection of capsaicin involves no tissue injury and evokes a pain that peaks after 5–15 s and disappears 10–30 min later.[28] We believe that our model falls in between these extremes, where central hyperexcitability may be partially dependent on generator input; that is, with little or no generator input the central hyperexcitability will be reduced, but may persist for a period of time.

Another important factor of variation between models is the duration of afferent activity capable of inducing central hyperexcitability. In some models, the duration of afferent activity capable of evoking central hyperexcitability is very restricted, *e.g.*, induction by electrical activation of afferent C-fibers detached from the periphery.[26] However, in the current model and probably in most clinical trauma situations, the injury may induce prolonged C-fiber activity that is capable of inducing central hyperexcitability beyond the time of injury, as documented in the current and other studies by development of secondary hyperalgesia after restitution of afferent conduction after local anesthesia.[2,18,19,29] Such prolonged capability of inducing central hyperexcitability is likely to explain the limited

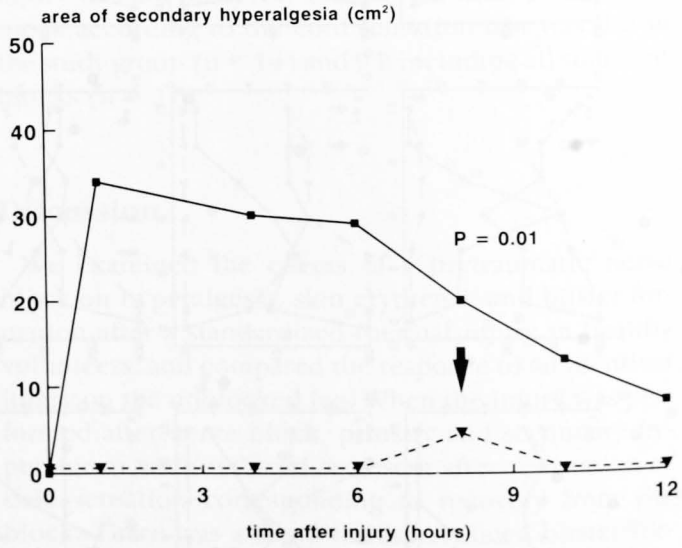

Fig. 3. Area of secondary hyperalgesia to pinprick (von Frey, 175 mN). Presented values are medians for the 14 subjects with sufficient blocks lasting less than 12 h. Dotted line = legs with block; full-drawn line = unblocked legs. The arrow indicates the median return of cold sensation. Time 0 h indicates observation before thermal injury. *P* value represents difference between legs after resolution of the nerve block.

or lack of effects of preemptive nerve blocks in clinical studies.[10,11] The principle of preemptive analgesia seems most valuable in situations where maintenance of central hyperexcitability is independent of continuous afferent input. Central mechanisms also may be necessary to explain the magnitude of the sensory changes in the area of primary hyperalgesia.[30] Kilo *et al.* recently concluded that hyperalgesia to punctate stimuli (von Frey bristle) is caused by central nervous plasticity rather than nociceptor sensitization.[3] Therefore, reduced central hyperexcitability may contribute to the attenuation of primary hyperalgesia observed in our study.

Duration of Block

The duration of the local anesthetic block, according to the cold sensation test, was surprisingly long, because the expected clinical duration of a nerve block with 9 ml lidocaine 1% is 1–2 h.[31] It cannot be excluded that a residual C-fiber block reduced hyperalgesia after return of cold sensation, because cold sensation is mediated by thin myelinated Aδ-afferents.[32] However, the susceptibility of thin Aδ- and C-fibers for local anesthetics are very similar and some C-fibers may even be slightly more resistant than the thinnest Aδ-fibers.[33,34] This may explain that a few subjects (3 of 6 possible) had secondary hyperalgesia to punctate stimuli, which is C-fiber-mediated,[3] in areas with abolished cold sensation, suggesting C-fiber activity in areas with blocked Aδ-fibers.

Effect of Block on Inflammation

Diminished neurogenic inflammation may explain the trend toward reduced blister formation and reduced hyperalgesia if these phenomena are dependent on neurogenic inflammatory mediators and the presence of these mediators is reduced by a nerve block. This would indicate that the local inflammatory response is modulated by efferent activity from the central nervous system. However, reduced local inflammatory response by nerve block is questionable, because little or no evidence supports this directly, except for a study in which a nerve block was shown to inhibit the local release of substance P after a heat injury of the rat paw.[35]

Peripheral denervation, a condition with some similarities to nerve block, potentiated edema after formalin injection in a rat paw 24 h after injury, whereas a significant antiedematous effect was demonstrated in the early postinjury period (1–5 h).[36] Denervation itself has been shown to induce edema and neutrophil infiltration in rat paw with onset about 10 h after denervation.[37] Recently, dorsal rhizotomy was shown to reduce joint inflammation 8 h after intraarticular injection of kaolin and carrageenan,[38] although no information was available about the late (*e.g.*, after 24 h) response. These and other studies[39] suggest that the early phase of inflammation (edema) may be reduced by denervation, whereas the late response may be aggravated. These results suggest that both proinflammatory and antiinflammatory mediators may be released from local nerve fibers. Whether these responses are purely local or under central nervous control, is unanswered.

In the classic works on neurogenic inflammation in humans, Lewis *et al.* never demonstrated any effect of a nerve block on local inflammation (*i.e.*, wheal and flare responses) after multiple stimuli.[40] Using the current burn model, we have shown that neither topical lidocaine and prilocaine (EMLA, Astra, Södertälje, Sweden) nor local infiltration with bupivacaine reduced the local inflammatory response.[41] In the current study, the local anesthetic was administered about 10 cm from the burned area, making a direct effect of the local anesthetic on injured tissue unlikely.

Reduced local inflammatory response by nerve block therefore is questionable, but our finding of a trend toward reduced blister formation ($P = 0.07$) indicates that the clinical importance of neurogenic inflammation in acute trauma requires further study.

In summary, our data suggest that a prolonged block may reduce late postburn primary and secondary hyperalgesia beyond the duration of the block. The study does not indicate whether the effect of the nerve block was related to the timing of the block in relation to the injury, because a postinjury block was not tested. Future studies should focus on the effects of prolonged nerve blocks on early and late pain after surgical trauma.

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