Effect of preoperative extradural bupivacaine and morphine on stump sensation in lower limb amputees

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Summary
We have examined the effect of preoperative extradural bupivacaine and morphine on post-operative stump sensation in 31 patients undergoing amputation of the lower limb in a prospective, randomized, double-blind study. Patients were allocated randomly to one of two groups: group 1 received extradural 0.25% bupivacaine 4–7 ml h−1 and morphine 0.16–0.28 ml h−1 before and during operation; group 2 received extradural saline before and during amputation and conventional analgesics for pain treatment. All patients received general anaesthesia for the amputation and extradural bupivacaine and morphine after operation. Sensory examination of the limb/stump was carried out before amputation, and after 1 week and 6 months. The following were measured: pressure pain thresholds (pressure algometry), touch and pain detection thresholds (von Frey hairs), thermal sensibility (thermal rolls), and allodynia and wind-up-like pain. There were no differences between the two groups at any of the postoperative assessments for mechanical and thermal sensibility or rate of allodynia and wind-up-like pain. Our study suggests that preoperative and intraoperative extradural block had no long-term prophylactic effect on hyperalgesia, allodynia or wind-up-like pain. (Br. J. Anaesth. 1998; 81: 348–354).

Keywords: analgesic techniques, extradural; anaesthetics local, bupivacaine; analgesics opioid, morphine; surgery, amputation; pain, phantom limb

Pain after amputation is a significant problem among amputees. Approximately 60–70% of amputees suffer from phantom pain in the first year after amputation. The mechanisms underlying pain in amputees are not clear but experimental and clinical evidence suggests that sensitization of central neurones before and during amputation may play a role. Previous studies have shown that phantom pain is more likely to be present in amputees who had severe pain in the limb before amputation compared with those with less severe pain. In a recent prospective study of 56 patients undergoing amputation, intense pain before amputation was associated with phantom pain in the first 6 months after amputation, and stump and phantom pain were significantly related 1 week after amputation. Some studies have reported that phantom pains are similar to previously experienced pains in a high proportion of amputees suggesting that pain experienced before amputation creates an imprint in pain memorizing structures in the central nervous system (CNS). Taken together these findings suggest that long-term and intense noxious input from the periphery may induce changes in the CNS resulting in sensitization and chronic pain.

The manifestations of sensitization include, apart from pain, reduction in pain threshold (hyperalgesia), evocation of pain, by non-noxious stimuli (allodynia) (for review see Willis) and pain elicited by repeated pricking stimuli (wind-up-like pain). Consistent with this are reports of abnormal stump sensibility in 50% of amputees and descriptions of wind-up-like pain in amputees.

Central sensitization after persistent noxious input raises the question of whether or not such neuronal hyperexcitability can be prevented. Several studies support the notion that signs of hyperexcitability after experimental nerve injury can be reduced by various treatments before or during injury. Clinical correlate to such pre-emptive effects was the observation that preoperative extradural block prevented phantom pain. However, not all studies support this finding. In a recent study, extradural bupivacaine and morphine administered for 18 h before, during and after amputation failed to reduce the rate and intensity of phantom pain in the first year after amputation.

Previous clinical studies have suggested that it is possible to prevent signs of hyperexcitability other than pain by preoperative or intraoperative treatment. For example, Richmond, Bromley and Woolf found lower pain sensitivity around the wound in 15 patients who received morphine before hysterectomy compared with 12 patients who received morphine after operation. While these studies suggest that intense treatment may reduce hyperexcitability in the early postoperative period, there is limited evidence for a reduction in long-term hyperexcitability. This is important because some surgical procedures, such as amputation, mastectomy and thoracotomy, are often associ-
ated with long-term pain, allodynia, hyperalgesia and wind-up-like pain.22–25 Therefore, we have examined, in a prospective, randomized, double-blind study, if extradural pain treatment started before amputation and continued into the postoperative period would reduce mechanical and thermal hyperalgesia, allodynia and wind-up-like pain 1 week and 6 months after amputation.

Patients and methods

Patients were recruited from 60 patients who took part in a major study of the effect of extradural bupivacaine and morphine in the prevention of stump and phantom pain after amputation.19 All were invited to participate in sensory testing of the stump, in addition to answering questionnaires on pain. Inclusion criteria were age more than 18 yr and undergoing amputation of the lower limb. Exclusion criteria were acute amputation, ipsilateral re-amputation, amputation of the foot or toes only, extradural pain treatment started before inclusion, dementia and contraindications to placement of an extradural catheter or combined extradural and general anaesthesia. Informed written consent was obtained from patients and approval was obtained from the regional Ethics Committee and the Danish National Board of Health.

Patients were allocated randomly to one of two groups of equal size. Group 1 (active treatment group) received extradural bupivacaine and morphine before and during amputation and group 2 (control group) received extradural saline and oral–i.m. morphine. Details of randomization have been described previously18 but briefly patients were stratified on the basis of the intensity of pain before amputation: the first patient entering the study with a pain intensity of 5–20 mg, 4–6 times a day, and 5–10 mg on demand was assigned to the opposite treatment from placement of the extradural catheter or combined extradural and general anaesthesia. Informed written consent was obtained from patients and approval was obtained from the regional Ethics Committee and the Danish National Board of Health.

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limb was recorded. In the operating theatre, pain was assessed by recording mean pain intensity experienced from the time of placement of the extradural catheter until amputation, and at the postoperative interviews, intensities of stump and phantom pain were recorded.

**Sensory testing**

On the day before amputation (before randomization and before placement of the extradural catheters) pressure pain thresholds, touch and pain detection thresholds, and thermal sensibility were measured. In the operating theatre and after administration of the bolus dose of bupivacaine, pressure pain thresholds were measured. After 1 week and 6 months, pressure pain thresholds, touch and pain detection thresholds, and thermal sensibility were recorded. Also, after 6 months, rates of allodynia and wind-up-like pain were examined. Measurements were performed at the lateral aspect of the limb/stump. If amputation was performed at the thigh or knee, the L2–3 dermatome was examined (above m. vastus lateralis) and if amputation of the calf was performed, the L4 dermatome was examined (above m. tibialis anterior).

**Pressure sensibility**

Pressure pain threshold (PPT) was determined using a hand-held electronic pressure algometer (Somedic AB, Sweden). The procedure has been described previously. Briefly, a circular probe with an area of 1 cm$^2$ was used. The pressure application rate was 20 kPa s$^{-1}$. The patient was told to say “stop” when a sensation of pressure changed to a sensation of pain. This was recorded as PPT and the value on the digital display was read by the examiner. Each value was determined three times with an interval of at least 30 s.

**Tactile sensibility**

Tactile sensibility was determined using von Frey hairs, consisting of 20 monofilaments of increasing diameter calibrated to deliver a specific force on the skin (Semmes-Weinstein monofilaments, Stoelting, IL, USA). The filaments were applied in an ascending and descending order of magnitude. The force required to bend the filament at the touch detection threshold (TDT) and at the pain detection threshold (PDT) was recorded.

**Thermal sensibility**

Thermal sensibility was examined using thermal rollers. The rollers were made of steel with steel handles. Sensibility to cold was examined with a thermal roller cooled in a box filled with ice. Sensibility to cold was examined with a thermal roller. The rollers were made of steel with steel handles. Sensibility to cold was examined with a thermal roller cooled in a box filled with ice. Sensibility to cold was examined with a thermal roller cooled in a box filled with ice.

**Wind-up-like pain**

Wind-up-like pain was carried out using a procedure described previously by Eide and colleagues. The skin was pricked repeatedly with a von Frey filament (6.65 units = 447 g) at a rate of 3 s$^{-1}$. The stimulation was not painful initially but after a few seconds the patients reported a marked increase in pain. Stimulation was continued for 30 s but discontinued before if the pain became unbearable. Five sites on the stump were stimulated: one site at the end of the stump, and anterior and posterior sites on the lateral and medial aspect of the stump. Wind-up-like pain was considered present if pain could be elicited at least one site of the stump.

**Alldynia**

Alldynia was determined by a von Frey hair at the touch detection threshold. The monofilament was moved along the stump and alldynia was considered present if sensation changed from a feeling of touch to a clear sensation of pain.

**Statistical analysis**

Results are presented as mean (sd) or median (range). The Mann–Whitney rank sum test was used to analyse differences between medians. Differences between the two groups in postoperative values of PPT, TDT and PDT were analysed as follows: for each patient a standardized value, postoperative/preoperative, was calculated. The standardized values in the two groups were compared on a logarithmic scale (i.e. the values were log-transformed and the mean values in the two groups were compared using a t test and 95% confidence intervals for the difference between means). The estimated mean difference and confidence interval were then transformed back to the original scale, yielding an estimate and 95% confidence interval of the median ratio between the standardized values in the two groups. Fisher’s exact test was used to compare rates of alldynia and wind-up-like pain in the two groups. $P<0.05$ was considered significant.

**Results**

Forty-five patients agreed to participate in sensory examination of the stump: 23 patients in group 1 and 22 in group 2. There were no differences between patients who agreed to take part in sensory testing and those who refused, in age, sex distribution or intensity of pain before amputation (data not shown). There were 31 patients at the 6-month interview: two patients (one from each group) were withdrawn from the study before amputation (in one patient the extradural catheter was displaced accidentally and the other patient only underwent toe amputation); three patients underwent re-amputation (all belonged to group 1) and nine patients died (four in group 1 and five in group 2). Patient characteristics and surgical details are shown in table 1.

**Perioperative pain, and stump and phantom pain after amputation**

**Perioperative pain**

Median duration of preoperative extradural block (group 1) was 16.5 (range 12–45) h and median duration of postoperative extradural pain treatment (both groups) was 214 (14–756) h.
There was a highly significant difference in pain experienced at the time from placement of the extradural catheter until amputation, between the extradural block and extradural saline groups ($P<0.001$). Eleven of 14 patients in group 1 were pain-free after the extradural pain treatment and scored 0 on a VAS. Two patients continued to have slight and intermittent pain (VAS scores 2 and 4). One patient continued to feel pain despite the extradural treatment. Median intensity of pain in group 1 was 0 (range 0–31). All patients in group 2, except one, had pain during the time from placement of the extradural catheter until amputation. Median pain intensity was 29 (0–80).

**Postoperative stump and phantom pain**

Details on stump and phantom pain have been presented previously. Briefly, there was no difference between the groups at the postoperative interviews when comparing rates of phantom pain. After 1 week the percentage of patients with phantom pain was 57.1% in group 1 and 58.8% in group 2. After 6 months the corresponding values were 78.6% and 58.8% in groups 1 and 2, respectively. Intensities of stump and phantom pain were also similar in the two groups (data not shown).

**SENSORY TESTING**

It was not possible to perform all types of sensory testing in all patients at all postoperative assessments, mainly because of lack of consent. Obvious contraindications to examination such as delayed healing and infection of the stump occurred in a few cases.

**Block before amputation**

PPT was examined in 22 patients (nine in group 1 and 13 in group 2) after the bolus dose of bupivacaine in the operating theatre. PPT was not reached by any patient in group 1. To avoid damage to the skin, a cut-off point for PPT was set at twice the value obtained on the day before amputation. Median PPT was 400 (range 300–650) kPa in group 1 and 238 (75–600) kPa in group 2 ($P<0.0001$). The degree of motor block after the bolus dose of bupivacaine before amputation, assessed using the Bromage scale (group 1), was complete (100%) in one patient (unable to move legs or feet), almost complete (66%) in 11 patients (unable to flex knees, but with free movement of feet) and partially complete (33%) in two patients (just able to flex knees, free movement of feet).

**Pressure and tactile sensibility**

PPT was examined in 18 patients (seven in group 1 and 11 in group 2) on the day before amputation and after 1 week and 6 months. Before amputation, median PPT was 227 kPa in group 1 and 195 kPa in group 2. Figure 1 shows the postoperative PPT values in the two groups. The standardized value, postoperative/preoperative PPT, is presented for each patient. After 1 week the standardized PPT values in group 1 were, on average, 0.59 times the standardized PPT values in group 2 (95% CI 0.21 to 1.66; $P=0.3$). After 6 months the standardized PPT values in group 1 were, on average, 0.51 times the standardized PPT values in group 2 (95% CI 0.24 to 1.1; $P=0.08$).

TDT and PDT were measured in 16 patients (seven in group 1 and nine in group 2). Median TDT and PDT were 0.41 g and 8.51 g, respectively, in group 1 before amputation; corresponding values were 8.51 g and 75.8 g in group 2. Postoperative TDT and PDT values are shown in figure 2. The standardized values, postoperative/preoperative TDT and PDT, are presented for each patient. After 1 week the standardized TDT values in group 1 were, on average, 1.0 times the standardized TDT values in group 2 (95% CI 0.78 to 1.3; $P=0.9$) and the standardized PDT values in group 1 were, on average, 1.3 times the standardized values in group 2 (95% CI 1.0 to 1.6; $P=0.09$). After 6 months the standardized TDT values in group 1 were, on average, 1.2 times the standardized TDT values in group 2 (95% CI 0.89 to 1.59; $P=0.2$) and the standardized PDT values in group 1 were, on average, 1.2 times the standardized values in group 2 (95% CI 0.97 to 1.38; $P=0.09$).

**Thermal sensibility**

In 15 patients (six in group 1 and nine in group 2), thermal sensibility was measured before amputation, and after 1 week and 6 months. Thermal sensibility
was similar in the two groups both before and after amputation. Also, postoperative thermal sensibility was not different from thermal sensibility before amputation (fig. 3).

Wind-up-like pain and allodynia

At the 6-month interview, 19 patients (10 in group 1 and nine in group 2) were examined for wind-up-like pain. Wind-up-like pain was elicited in 11 patients, eight in group 1 and three in group 2 (P = 0.07).

The incidence of allodynia was examined in 28 patients after 6 months (12 in group 1 and 16 in group 2). Allodynia was present in nine patients: four in group 1 and five in group 2 (ns). There was no difference between rates of allodynia and wind-up-like pain in the two groups (table 2).

Discussion

In this prospective, randomized study, we found no effect of intense preoperative and intraoperative extradural block on postoperative stump sensibility to mechanical and thermal noxious and non-noxious stimuli. Therefore, our findings suggest that extradural analgesia does not prevent late signs of hyperexcitability at the level of the stump. However, before accepting this notion, some points need consideration.

First, it may be argued that selection bias and a limited number of patients were responsible for our negative findings. Although selection bias cannot be excluded, patient characteristics were similar in those who agreed to participate in sensory testing and those who refused. The fact that there was no consistent trend towards an effect of extradural block on stump sensibility after amputation suggests that our failure to find an effect cannot be explained by the small number of patients.

Second, it is possible that central sensitization was not present and therefore could not be blocked. However, pressure pain thresholds were reduced after amputation, and allodynia and wind-up-like pain were present in a relatively large proportion of patients in the block and non-block groups, thus indicating that sensitization to mechanical stimuli was present and amenable to block.

Third, it is also unlikely that our failure to see an effect was a result of selection of stimuli or stimulation of receptors unresponsive to sensitization. We assessed both thermal and mechanical modalities, in addition to different types of mechanical stimuli. Therefore, it is likely that afferent input via C-mechano-heat receptors and low threshold mechano-receptors conveyed by C, Aδ and Aβ fibres, respectively, were examined in this study.

The discrepancy between our findings and those reported in experimental and clinical studies may have several explanations. In experimental studies on the effect of treatment before injury, conditioning stimuli are usually of short duration and may consist of brief C-fibre stimulation, and localized mechanical, thermal or chemical injury.

In studies in human volunteers, different methods of producing hyperalgesia (e.g. localized burn injury or intradermal or topical application of capsaicin) have been used, characterized by producing an afferent C-fibre volley of intense but short duration.

Table 2 Incidence of wind-up-like pain and allodynia 6 months after amputation (number (%))

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<th>Wind-up-like pain</th>
<th>Allodynia</th>
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<tr>
<td>Group 1</td>
<td>8 of 10 (80%)</td>
<td>4 of 12 (33.3%)</td>
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<tr>
<td>Group 2</td>
<td>3 of 9 (33.3%)</td>
<td>5 of 16 (31.3%)</td>
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Figure 2 Touch and pain detection thresholds (TDT and PDT) after 1 week and 6 months for groups 1 (n = 7) and 2 (n = 9). The standardized values, postoperative/preoperative TDT and PDT, are shown for each patient.

Figure 3 Thermal sensibility in the range 0–45 °C before (A), and 1 week (B) and 6 months (C) after amputation for groups 1 (n = 6) and 2 (n = 9). All sensations were described on a scale from 1 to 9 (1 = painful heat, 2 = very warm, 3 = warm, 4 = slightly warm, 5 = neutral, 6 = slightly cold, 7 = cold, 8 = very cold, 9 = painfully cold). Values are medians.
In contrast, the nociceptive barrage of the CNS in patients undergoing amputation is intense and long-lasting. We propose that the extradural block in our study was insufficient to block afferent C-fibre input and hence reduce central sensitization. This notion is supported by previous studies. It has been shown that a lumbar extradural block with bupivacaine did not completely prevent impulses, as assessed by somatotopically evoked potentials, in reaching the CNS. Furthermore, Dahl and colleagues found that a short-lasting block of the skin with lidocaine before experimental burn injury postponed but did not prevent secondary hyperalgesia. It may be impossible to prevent afferent input from reaching the CNS during surgery but we cannot exclude the fact that other forms of regional analgesia would be able to influence central sensitization.

Clinical studies have not provided consistent results. In the study of Richmond, Bromley and Woolf, patients undergoing hysterectomy were allocated randomly to one of three groups: morphine 10 mg i.m., 1 h before operation (i.m. pre) (n = 8), morphine i.v. at induction of anaesthesia (i.v. pre) (n = 7) or morphine i.v. at closure of the peritoneum (i.v. post) (n = 12). Pain sensitivity around the wound, as assessed by von Frey hair, was reduced after 24 and 48 h in both preoperative treatment groups compared with the i.v. post group. Tverskoy and colleagues found that pre- and intraoperative administration of morphine (n = 9) or ketamine (n = 9) reduced the intensity of pain to suprathreshold pressure on the wound 48 h after hysterectomy. The effect of ketamine on postoperative hyperalgesia was studied and the area of hyperalgesia was reduced in 10 patients who received ketamine during and for 72 h after nephrectomy compared with 10 patients who received placebo. Johansson and colleagues examined 66 patients undergoing cholecystectomy. The abdominal wall was infiltrated with ropivacaine or saline before surgical incision. The pressure exerted to reach maximum pain tolerance was assessed at intervals for 7 days after operation. The only difference between the two groups was after 6 h, which could be explained by a residual effect of ropivacaine.

The difference between our results and those of others may have several explanations. Other workers have studied only early postoperative hyperalgesia, and differences in the extent of surgical trauma, patient categories and methods of assessment may also play a role. The positive findings in the study by Stubhaug and colleagues may be explained by the use of an N-methyl-D-aspartate (NMDA) receptor antagonist as the NMDA receptor is known to be involved in central hyperexcitability.

After amputation, neuromas of the nerve endings are formed. Such neuromas display a series of abnormalities, including spontaneous activity and increased sensitivity to chemical, mechanical and metabolic factors. Axotomized cell bodies in dorsal root ganglia may also show abnormal spontaneous activity so that dorsal horn neurones receive abnormal input from axotomized nerve endings and from sensitized dorsal root ganglion cells. In our study, it is likely that the afferent barrage from the periphery outlasted postoperative extradural block and thus induced or maintained central sensitization before the early postoperative period.

In summary, while there is circumstantial evidence from experimental and clinical studies that analgesic treatment before injury prevents pain and hyperalgesia, our study suggested that preoperative and intraoperative extradural block had no long-term prophylactic effect on hyperalgesia, allodynia and wind-up-like pain.

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