The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial


Summary

Background Postherpetic neuralgia is the most frequent complication of herpes zoster. Treatment of this neuropathic pain syndrome is difficult and often disappointing. We assessed the effectiveness of a single epidural injection of steroids and local anaesthetics for prevention of postherpetic neuralgia in older patients with herpes zoster.

Methods We randomly assigned 598 patients older than 50 years, with acute herpes zoster (rash <7 days) below dermatome C6, to receive either standard therapy (oral antivirals and analgesics) or standard therapy with one additional epidural injection of 80 mg methylprednisolone acetate and 10 mg bupivacaine. The primary endpoint was the proportion of patients with zoster-associated pain 1 month after inclusion. Analyses were by intention-to-treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN32866390.

Findings At 1 month, 137 (48%) patients in the epidural group reported pain compared with 164 (58%) in the control group (relative risk [RR] 0·89, 95% CI 0.71–0.97, p=0.02). After 3 months these values were 58 (21%) and 63 (24%) respectively (0.89, 0.65–1.21, p=0.47) and, at 6 months, 39 (15%) and 44 (17%; 0.85, 0.57–1.13, p=0.43). We detected no subgroups in which the relative risk for pain 1 month after inclusion substantially differed from the overall estimate. No patient had major adverse events related to epidural injection.

Interpretation A single epidural injection of steroids and local anaesthetics in the acute phase of herpes zoster has a modest effect in reducing zoster-associated pain for 1 month. This treatment is not effective for prevention of long-term postherpetic neuralgia.

Introduction Postherpetic neuralgia is the most frequent complication of herpes zoster. The reported incidence of postherpetic neuralgia is 9–34%, depending on the definition.1 Postherpetic neuralgia can negatively affect quality of life, because many patients develop severe physical, occupational, and social disabilities as a consequence of their chronic pain.1 Once the syndrome has developed, the effect of treatment is disappointing.7

Therefore, the importance of preventive strategies for postherpetic neuralgia is widely recognised.1 Although the effectiveness of a varicella-zoster vaccine on prevention of zoster-related morbidity is promising,7 postherpetic neuralgia will remain a serious problem for many years. Antiviral therapy can shorten the duration of zoster-associated pain, but many patients with herpes zoster develop postherpetic neuralgia despite such treatment.12 As herpes zoster goes together with local inflammation of the dorsal root ganglion, and this inflammation is considered to be an important causative factor for postherpetic neuralgia,14 interventions can be aimed at reducing this inflammation.14 One such intervention is the epidural administration of corticosteroids and local anaesthetics. In this respect, Pasqualucci and colleagues11 considered to be an important causative factor for postherpetic neuralgia,8,9 interventions can be aimed at reducing this inflammation.10 One such intervention is the epidural administration of corticosteroids and local anaesthetics. In this respect, Pasqualucci and colleagues11

Methods Patients The study design has previously been published and discussed.16,17 Briefly, 300 family doctors in different regions of the Netherlands recruited patients from September, 2001, to February, 2004. Inclusion criteria were herpes zoster within 7 days after onset of the rash, dermatome below C6, age older than 50 years, sufficient command of the Dutch language, and willingness to comply with the allocated treatment and follow-up measurements. Exclusion criteria were coagulation abnormalities including use of coumarin anticoagulants (salicylates were allowed), bacterial infection of the skin overlying the vertebra of the affected dermatome, allergy to methylprednisolone or bupivacaine, and known serious immune disorders (eg, AIDS). Before treatment
allocation all patients gave written informed consent. The medical ethics committee of the University Medical Center Utrecht approved the study protocol.

Procedures
Baseline measurements included pain duration, severity and localisation of the rash, co-morbidity, and drug use. The patient was asked to quantify his/her average pain in the last 24 hours using a visual analogue scale (VAS) ranging from “no pain” at 0 mm to “worst pain ever experienced” at 100 mm. After this, the doctor called the study centre. An administrative assistant immediately randomised the patient using a computer program with block randomisation.

Patients randomised to the control group received the current standard treatment for herpes, consisting of analgesics as needed and antiviral medication if the rash had been present for less than 72 h.\(^14\) The family doctor was free to select either acyclovir (800 mg five times daily), famciclovir (500 mg three times daily), or valaciclovir (1000 mg three times daily), each administered orally for 7 days.

Patients allocated to the epidural injection group also received the abovementioned standard treatment. Additionally, they were referred to their local hospital for a single epidural injection. Anaesthetists in the 22 cooperating hospitals had agreed to give this injection within one working day after inclusion. The epidural space was located using either the loss of resistance or the hanging drop technique at the spinal level corresponding to the implicated dermatome.\(^15\) A mixture of 80 mg methylprednisolone acetate and 10 mg bupivacaine (0-25% weight/volume) was injected epidurally. The procedure was repeated if no sensory loss in the relevant dermatome was detected 30 min after injection; this action was necessary in seven patients.

The primary endpoint was the presence of zoster-associated pain 1 month after inclusion. Presence and severity of pain at other time points were secondary endpoints. Patients recorded the presence of pain by answering the question “do you have shingles-related pain today? Yes/No” on a mailed questionnaire. They were also asked to assess the severity of their pain in the past 24 h on a 0–100 mm VAS. The questionnaires were completed once a week during the first month after inclusion, and at 2, 3, and 6 months. Side-effects were recorded at 1 month. If a questionnaire was not received at the study centre within the allocated time, the research assistants tried to complete the form by means of a telephone interview. The family doctors recorded all interventions aimed at treatment of zoster-associated pain (prescription of analgesics, physiotherapy, etc) during the 6 months of follow-up. Data entry was done by administrative assistants, blinded to the assigned treatment.

Statistical analysis
Based on an \(\alpha\) of 5% and 80% power, we calculated that 250 patients were needed in each treatment arm to detect a clinically relevant reduction in the incidence of zoster-associated pain 1 month after the onset of the zoster rash from 12% to 5%. Although earlier studies showed an incidence of postherpetic neuralgia of 9–34% when using standard treatment,\(^1\) we used a more conservative incidence to be expected in our control group based on data from a pilot study.\(^3\) Allowing for 10% loss of follow-up, the required number of study patients was 550.

Analyses were carried out with an intention-to-treat approach. The presence of pain (at the different time points) in the two groups was compared by calculating the relative risks (RR) with 95% CI and tested with the \(\chi^2\) test. An additional per-protocol analysis was done to evaluate the preventive effectiveness of the intervention with regard to the actual treatment received. Differences in VAS scores (at different time points) with regard to pain intensity were analysed between the two groups for all patients, as well as for those who actually reported pain, using a Mann-Whitney test.

To account for the fact that all outcomes were repeatedly measured during the 6 months we also did a repeated measurement analysis, using a random effects Generalized Linear Mixed Models in SAS for Windows (version 8.2; Proc Genmod and Proc Mixed). Finally, we repeated the analyses after imputation of missing outcome data (5% for the primary endpoint) by means of linear regression modelling. Such a model predicts the value of a missing variable, by using all available data for that patient.

Because age, baseline intensity of pain, and rash severity are the most important risk factors of

<table>
<thead>
<tr>
<th>Table 1: Patients’ characteristics at inclusion</th>
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<tr>
<td><strong>Assigned to standard group</strong></td>
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<tr>
<td>(n=297)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
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<tr>
<td><strong>Age</strong></td>
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<td>Years</td>
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<tr>
<td><strong>Localisation</strong></td>
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<tr>
<td>Cervical</td>
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<td>Thoracic</td>
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<td>Lumbar</td>
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<tr>
<td>Sacral</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
</tr>
<tr>
<td>Severity (mm on VAS)</td>
</tr>
<tr>
<td>Duration (days)</td>
</tr>
<tr>
<td><strong>Number of skin lesions</strong></td>
</tr>
<tr>
<td>0–20</td>
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<tr>
<td>21–46</td>
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<tr>
<td>(&gt;47)</td>
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<tr>
<td>Unknown</td>
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<tr>
<td><strong>Duration of rash</strong></td>
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<tr>
<td>Days</td>
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</table>

Values are number of patients (%); continuous values are median (25th–75th percentile).
postherpetic neuralgia and thus potential confounders in the association under study,\(^1,1^4,1^8\) we planned a priori to undertake an adjusted (multivariate logistic regression) analysis (for the outcome: pain, yes or no) and a subgroup analysis, regarding these three factors.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN32866390.

**Role of the funding source**

The funding source had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

Figure 1 shows the number of patients screened and included in the trial, between September, 2001, and February, 2004, by 300 family doctors. Age and intensity of pain of the included patients were similar to the age and pain intensity of the herpes zoster patients who met the inclusion criteria but were not included. Baseline characteristics of the included patients are summarised in table 1. The median VAS score of pain intensity at baseline was slightly lower in the control group than in the epidural group (table 1). After 1 month, ten patients (3%) in each group were lost to follow-up. Three patients randomised to the control group (mean VAS 33 mm) requested and received an epidural injection, and 27 patients in the epidural group (mean VAS 35 mm) changed their minds when confronted with the result of randomisation and refused the injection.

1 month after inclusion, fewer patients in the intervention group reported zoster-associated pain than in the control group (RR 0·83, 95% CI 0·71–0·97, p=0·02, table 2). The risk difference was −10%; the number needed to treat was ten (ie, for every ten patients who receive epidural injection, one of them would be free from zoster-associated pain within 1 month of injection compared with patients who receive standard therapy only). The relative risk did not alter when analysed by the actual treatment received. In the subgroup analyses according to patients’ age, severity of pain, and skin rash at study entry, the relative risks for pain at 1 month after inclusion did not differ from each other or from the overall estimate.

After adjustment for age, baseline VAS, and rash severity, the RR for zoster-associated pain at 1 month for patients with an epidural injection versus standard therapy only was 0·81 (95% CI 0·69–0·95), compared with 0·83 unadjusted (table 2). Repeated measurement analysis and repetition of all analyses after imputation of the missing data did not alter the results. If a threshold of VAS greater than 30 mm was applied, in order to measure only pain that is judged to be clinically relevant,\(^1^9\) the number of patients with pain dropped to 58 (21%) in the intervention group and 74 (26%) in the control group (0·78, 0·58–1·06, p=0·11).

Figure 2 shows the resolution of pain in the first 6 months. In the first 4 weeks, the incidence of pain was significantly reduced in the intervention group. At 3 months, 58 (21%) patients in the intervention group reported zoster-related pain, compared with 63 (24%) in the control group (0·89, 0·65–1·21, p=0·47, table 2); at 6 months, 39 (15%) patients in the intervention group reported zoster-related pain, compared with 47 (18%) in the control group (0·85, 0·57 to 1·26, p=0·52, table 2).

### Table 2: Results at different times after inclusion

<table>
<thead>
<tr>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ZAP (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>164/283 (58%)</td>
<td>63/266 (24%)</td>
</tr>
<tr>
<td>Epidural</td>
<td>137/284 (48%)</td>
<td>58/275 (21%)</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0·85 (0·71 to 0·97)</td>
<td>0·89 (0·65 to 1·21)</td>
</tr>
<tr>
<td>RD (95% CI)</td>
<td>−9·7% (−17·9 to −1·5)</td>
<td>−2·6% (−9·6 to 4·4)</td>
</tr>
</tbody>
</table>

ZAP=zoster-associated pain. RD=risk difference. *Denominators equal number of patients in trial minus those with missing data.

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585 patients with HZ identified

655 patients did not meet inclusion criteria

51 met exclusion criteria

470 refused consent

98 physician declined to participate

83 unknown

1955 patients with HZ identified

598 patients enrolled

297 assigned to standard treatment

5 withdrew after randomisation

292 Baseline

5 lost to follow-up

287 1 month

2 lost to follow-up

284 3 months

3 lost to follow-up

280 6 months

301 assigned to standard treatment and epidural injection

3 withdrew after randomisation

298

2 lost to follow-up

294 4 withdrew after problems with injection

1 withdrew after other illness

291

2 lost to follow-up

287 2 withdrew after other illness

2 lost to follow-up

285

3 lost to follow-up

280 1 withdrew after other illness

Figure 1: Trial profile

HZ=herpes zoster. Three patients assigned to standard treatment received an epidural injection, and 27 patients assigned to standard treatment plus epidural treatment did not receive the injection.
6 months, these numbers were 39 (15%) and 44 (17%), respectively (0·85, 0·57–1·13, p=0·43; table 2). Figure 3 shows the time course of the intensity of pain in all patients. 1 month after inclusion, the median VAS score was 2 mm (25th–75th percentile 0–23) in the intervention group and 6 mm (0–32) in the control group (p=0·02). In the repeated measurement analyses there was no difference in the reduction of incidence or severity of pain over time between the groups (similar slopes in each group, figures 2 and 3). When patients without pain were excluded, the median VAS score at 1 month amounted to 25 mm (25th–75th percentile 9–50) in the intervention group and 22 mm (6–45) in the control group (p=0·55). Only at 1 week after inclusion did pain intensity in patients who reported having pain differ significantly between the groups: the median VAS score was 39 mm (25th–75th percentile 21–60) in the epidural group versus 49 mm (30–66) in the control group (p=0·001).

The number of re-interventions aimed at treatment of zoster-associated pain (drug prescription, physiotherapy, etc) did not differ significantly between the two treatment groups during the first month after inclusion, or during the next 5 months.

Of the 281 patients who received an epidural injection (277 in the injection group and four in the control group), 31 (11%) had one or more complaints that were potentially related to the intervention. These included six (2%) reports of dizziness, three (1%) of flushes, eight (3%) of headache, and 15 (5%) of backache. No major adverse events (dissemination of zoster, meningitis, epidural haematoma) were registered. Unintended perforation of the dura mater was not reported.

**Discussion**

The findings of this randomised study show that a single epidural injection with methylprednisolone and bupivacaine in acute herpes zoster reduces zoster-associated pain. Up to 1 month after inclusion, the number of patients reporting pain was significantly reduced. However, the effect of the epidural injection was strongest during the first week and did not last beyond 1 month. As the main clinical problem is long-lasting pain, the secondary endpoints (ie, pain for up to 6 months) are as important as the primary endpoint (pain at 1 month). Although there was a baseline imbalance between groups with respect to severity of pain, this difference had little effect on the results; the adjusted RR was similar to the unadjusted RR.

Although epidural injections have been used for decades both to treat zoster-associated pain and to prevent postherpetic neuralgia,13,20,21 the effectiveness of this treatment has not been previously assessed in a randomised clinical trial. Two recent reviews concluded that epidural local anaesthetics and corticosteroids reduce acute pain, but the results towards prevention of postherpetic neuralgia are contradictory.10,22 Both reviews emphasise the lack of randomised trials. Because large samples are needed, such trials require much effort. The primary care setting in the Netherlands was well suited to our trial. The high density of hospitals in the Netherlands allowed prompt treatment after referral by the family doctor. Participating hospitals did not need to have a specialised pain clinic, as virtually every anaesthetist is proficient in giving an epidural injection below C6 using the loss-of-resistance or hanging drop technique.17

**Generalisability of the results depends on whether the study patients were representative of all patients at risk. Because age and pain intensity were similar between included and non-included patients, the results of our study may indeed be generalised to the target population. Our study was designed for patients with herpes zoster below C6, because it is uncommon to give an epidural injection without fluoroscopy above this level. The results of this study, therefore, can only be applied for prevention of zoster-associated pain below C6,**
which occurs in about 75% of patients. Moreover, the study included only patients with acute zoster. Treatment of herpes zoster of duration longer than 1 week was beyond the scope of the study.

Trials that have soft endpoints such as pain are susceptible to a placebo effect. Nonetheless, we specifically opted for a pragmatic study design to measure the effectiveness that can be expected in a daily-care setting. If the aim had been to measure the efficacy (ie, the effect of the injected local anaesthetics per se), a placebo-controlled explanatory trial would have been more appropriate. We would have needed to give an epidural injection with saline in the control group, with the attendant increase in burden to patients and risks (eg, epidural haematoma, meningitis). We judged such a trial to be unethical. Moreover, blinding would be difficult to maintain because of the absence of immediate local anaesthesia after injection with placebo reveals the assigned therapy. Furthermore, if a placebo effect were present, it should be considered as part of the overall treatment effect, which will also be observed in future patients in daily care.

The incidence of zoster-associated pain at 1 month in the group with only standard treatment was 58%, a higher percentage than previously reported. These lower reported incidences were based on data from patients who attended their family doctor for persistent pain, whereas in the present trial we asked every patient about the presence of any pain and did not apply a threshold in pain intensity. If only pain above a threshold of 30 mm on the VAS is judged to be clinically relevant, the proportion of patients with zoster-associated pain in the control group drops to 26%, which is more in line with previous published work.

The postulated mechanism of action of the administered epidural drugs in herpes zoster is twofold: steroids reduce de-afferentiation by inhibition of inflammation and concomitant swelling-induced neural ischaemia, while local anaesthetics provide analgesia and sympathetic blockade, interrupting the process of sensitisation. Consequently, neural damage and subsequent neuropathic pain are reduced. For these processes to occur, the injected drugs must actually reach the target structures. In the present study, we chose to give a single epidural injection with the standard loss-of-resistance or hanging drop technique for localisation of the epidural space in the midline. These techniques require no special equipment and, for practical reasons, most anaesthesiologists prefer these techniques to an image-guided one. Although measuring sensory loss after injection confirms the proper deposition of the drugs in the epidural space, the administered drugs might still not have reached the affected dorsal root ganglion in sufficient quantities. It is conceivable that alternative techniques, such as injection under fluoroscopy, placement of an epidural catheter, use of higher injected volumes, or repeated injections might have a higher probability of reaching the target structures and, accordingly, result in increased effectiveness. One randomised trial assessed the effectiveness of epidural methylprednisolone and bupivacaine, administered repeatedly via an image-guided catheter for 7–21 days until the patient was pain free. The reported effectiveness of this procedure was higher than that observed in our study (RR 0·19 vs 0·83 for pain at 1 month). However, an epidural catheter for 1 or more weeks requires hospital admission, and entails a higher risk of side-effects such as infection and suppression of the adrenal cortex. Moreover, the costs are much higher.

To achieve an anti-inflammatory effect, oral steroids might also be considered. Two studies with high-dose prednisolone given for 21 days showed a modest reduction of acute pain but no effect on incidence of postherpetic neuralgia. In one of these studies, adverse side effects led the authors to conclude that oral steroids cannot be recommended for patients with herpes zoster.

We conclude that one epidural injection of methylprednisolone and bupivacaine, applied in the acute phase of herpes zoster, has a modest effect in reducing zoster-associated pain for 1 month. However, because this treatment did not prevent long-term postherpetic neuralgia, we suggest that an epidural injection of corticosteroid and bupivacaine only be considered for patients with severe acute pain from herpes zoster who are not responding to standard analgesic therapy.
References
