Clinical experience with intrathecal bupivacaine in combination with opioid for the treatment of chronic pain related to failed back surgery syndrome and metastatic cancer pain of the spine

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Abstract

Background context: Bupivacaine is a local anesthetic agent of the amide class. This drug has been used in many clinical situations including intrathecal infusion. The literature regarding intrathecal bupivacaine is limited to small case studies, and anecdotal reports. This article examines a large patient group receiving bupivacaine with opioids over an extended period of time and analyzes efficacy and safety. The patients had pain related to failed back surgery syndrome or metastatic cancer to the spine.

Purpose: The purpose of this study was to determine the efficacy and safety of intrathecal bupivacaine combined with opioids for treatment of pain of spinal origin when opioids alone were inadequate. The secondary purpose of this study was to determine if the combination of bupivacaine and opioids created a neurological safety risk.

Study design/setting: The study design was retrospective, and involved consecutive medical records review by a disinterested third party.

Patient sample: One hundred nine consecutive patients were studied for a total of 6,780 patient weeks of bupivacaine/opioid infusion. These data were compared with a comparable time in the opioid alone treatment arm. The population included 84 noncancer patients and 25 cancer patients.

Outcome measures: The primary outcome measure was pain relief obtained by a group of patients with a combination of bupivacaine and opioids as compared with opioid alone when delivered by intrathecal infusion. The visual analog scale was used to measure pain levels. Secondary objectives included measuring the amount of oral and transdermal medication required (opioid and nonopioid), emergency visits, routine office visits and patient satisfaction. These secondary objectives give a measure of health-care utilization. We also reviewed neurological complications during the combined arm of treatment.

Methods: The study was done retrospectively with 109 consecutive patients. Patient chart reviews were used to determine the visual analog scales, amount of oral opioids, oral nonopioid adjuvant and patient satisfaction ratings. Patient satisfaction and pain rating was measured by a visual analog scale. Other factors recorded were emergency room visits, doctor’s visits (other than the primary pain physician) and pain center visits. We also reviewed records for neurological deficits in the opioid arm and the combined arm. The \( t \) test was used to analyze statistical significance.

FDA device/drug status: Approved for this indication (Synchromed intrathecal pump, morphine and bupivacaine).

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Results: The findings suggested that in the combination arm the pain relief was significantly better (p=.008), the number of oral opioids used were significantly less (p=.008), the number of oral nonopioid adjuvants were reduced, the number of doctor’s visits were less in the combined arm (p=.008), the number of pain clinic visits were less (p=.03), the number of emergency visits were significantly less (p=.01) and patient satisfaction was better (p=.003). The total dose of morphine was reduced by 23% in the combined arm (p=.005). During the course of treatment with intrathecal bupivacaine, there were no irreversible complications.

Conclusion: Bupivacaine, when used in combination with opioids, is a helpful and safe method of treatment in a select population of patients who have not responded to intrathecal opioids alone. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Chronic pain; Intrathecal pumps; Intrathecal bupivacaine; Intrathecal morphine; Safety; Efficacy

Introduction

Bupivacaine hydrochloride is a local anesthetic agent of the amide class. This drug has been used for local infiltration, epidural infusion and spinal analgesia during surgical procedures, and continuous intrathecal infusion for chronic pain of cancerous and noncancerous origins. Results for treating pain of spinal origin have been favorable when delivered by epidural infusion [1].

Toxicologic studies in animals have demonstrated the safety of chronic intrathecal bupivacaine infusion in the rat model, rabbit model, dog model and cat model [2–5]. In one study, there was some mild neurologic toxicity with concentrations of bupivacaine that were much greater (approximately 100-fold) than the concentrations typically used in clinical practice [5]. Human studies in terminal cancer patients in which postmortem spinal tissue was evaluated histologically have revealed no neurotoxicity in patients receiving chronic infusion of opioids and bupivacaine for long periods of time [6]. The limited data available regarding safety in humans with chronic infusion using this drug combination have been favorable [7].

Intrathecal bupivacaine has been used clinically for many years. The most common use of bupivacaine in the neuraxis has been in the epidural space for postsurgical pain and obstetrical anesthesia. This article focuses on the safety and efficacy of intrathecal bupivacaine for treatment of spine pain related to failed back surgery or spinal metastasis.

Methods

A retrospective analysis was used to study 109 consecutive patients who received intrathecal bupivacaine in combination with opioids by means of an implantable infusion pump. All patients were on bupivacaine, and data were compared with equal percent of time before starting the combination treatment arm. Because these patients had all been initially treated with opioids alone, they served as a comparison group for both treatment arms. Each patient had a SynchroMed (Medtronic, Minneapolis, MN) infusion system placed for severe pain. Patients were screened by means of a continuous infusion technique by an epidural or intrathecal route before having the pump implanted. The patients in the noncancer group had back and leg pain after unsuccessful back surgery. The cancer patients had spine pain related to metastatic bone disease. All patients in the noncancer group were screened for psychological stability. The cancer patients did not undergo psychological clearance.

The delivery of chronic intrathecal infusions can be either by means of an externalized pump or more commonly through a subcutaneous implantable pump. Implantable pumps are manufactured in two classifications: constant flow and programmable. A constant flow pump delivers medication at a steady rate using a hydraulic driving force. Two such pumps are the Medtronic Isomed infusion system (Medtronic, Minneapolis, MN), and the Arrow (Medtronic, Minneapolis, MN) infusion system. These pumps have a prolonged life of the product, but because the flow rate is not adjustable, an invasive refill is required each time a dose adjustment is needed. Currently, only one programmable pump is Food and Drug Administration approved for human use, the Medtronic Synchronized EL pump. This pump allows dose changes to be made using noninvasive telemetry. The programmable technology requires an internal battery source that must be replaced intermittently. The pump has a battery life of approximately 7 years in most clinical applications. Both types of pumps are refilled percutaneously using a small-gauge needle. The intrathecal drug infusion pump of choice accesses the spinal fluid of the subarachnoid space by means of a catheter that is made of silastic or polyurethane. The pump and catheter combined comprise the drug infusion system. Intrathecal infusion has been found to lower the dose required to produce equipotent analgesia when compared with other routes of administration. This reduced dose requirement is associated with reduced side effects and complications [8].

Inclusion criteria required a pain score on the Visual Analog Scale (VAS) of greater than 6 on at least three consecutive visits while in the opioid alone treatment arm. Patients were not excluded based on opioids used by multiple routes. Patients were excluded from the study if pregnant or under 18 years of age. Patients were also excluded if they had any neurological complications during the opioid-alone phase of their treatment.

We reviewed previously recorded patient pain scores (VAS) at a minimum of three consecutive visits in each
treatment arm. We also reviewed the amount of oral opioids and nonopioid analgesic used, and frequency of doctor and emergency room visits. Opioid dosing was not quantified, but it was determined if the patient required oral or transdermal opioid supplementation. Nonopioid analgesics were recorded by class and included nonsteroidal anti-inflammatory agents, anticonvulsants, antispasmodics, antidepressants and other analgesics (ie, tramadol, barbiturates). Data were collected on the total number of drug classes taken. Patients were also asked to rate satisfaction during three consecutive visits in each treatment arm. These measurements were systemically recorded using a flow sheet. The scale used was 1 for very unsatisfied with treatment to 10 for very satisfied with treatment based on the VAS. Patients’ charts were reviewed for neurological findings before implantation of the device, during the opioid-only phase of treatment and during the opioid/bupivacaine treatment period. Time periods for observation in the opioid versus the opioid-bupivacaine treatment arm were matched in equal time. Changes in reflexes, sensation, motor strength, complaints from the patients of numbness, worsening function and bladder or bowel changes were evaluated. Any changes noted on magnetic resonance image (MRI) or electromyogram (EMG) were also noted. Disinterested third parties performed all chart reviews. The Student’s t test was used for statistical comparisons. P values less than .05 were considered statistically significant.

**Results**

In this study, patients’ ages ranged from 35 to 68 years, and the mean (±STD) age of the patient population was 51.6±16.2 years. The male to female ratio was 2:1. The mean weight was 192±32.1 pounds. Twenty-five patients (22.9%) were diagnosed with cancer, and 84 patients (77.1%) had noncancer diagnoses. The mean exposure to bupivacaine was 62.2±21.2 weeks in the total population. The data were compared with equal time of exposure to opioids alone in the same patient before adding bupivacaine. In the cancer population, the mean exposure was 28 weeks, and in the noncancer population the mean exposure was 102 weeks.

We found a significant improvement in pain scores in the bupivacaine-opioid (the combined arm) treatment arm versus the opioid-alone treatment arm. Pain relief scores (VAS) ranged from 0.0 to 6.4 during bupivacaine arm as compared with time-matched intervals for the opioid-alone phase. All but one patient experienced some reduction in pain with the addition of bupivacaine versus their baseline on opioid alone. The combined drug group also experienced a reduction in need of oral and transdermal opioid use (p=.03). Office visits were based on need for pain assessments per patient requests. The combined treatment group used less nonopioid medications overall, but the difference did not reach statistical significance. Table 1 gives an overview of these data.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Efficacy</th>
<th>Opioids alone (N = mean)</th>
<th>Opioids with bupivacaine (N = mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain relief (Visual Analog Scale)</td>
<td>6.4</td>
<td>3.2*</td>
<td></td>
</tr>
<tr>
<td>Satisfaction</td>
<td>6.3</td>
<td>9.1*</td>
<td></td>
</tr>
<tr>
<td>Oral transdermal opioids (classes per day)</td>
<td>3.2</td>
<td>1.1*</td>
<td></td>
</tr>
<tr>
<td>Doctor visits (per month)</td>
<td>3.4</td>
<td>0.2*</td>
<td></td>
</tr>
<tr>
<td>Other physicians (per month)</td>
<td>1.8</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>Emergency room visits (per month)</td>
<td>2.3</td>
<td>0.1*</td>
<td></td>
</tr>
<tr>
<td>Nonopioid medications (classes per month)</td>
<td>3.9 units</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

*Results are considered statistically significant.

We found that in 109 patients with 6,780 patient weeks of bupivacaine-opioid infusion there were no significant neurological sequelae from the use of bupivacaine. Two patients experienced mild paresthesias that dissipated once the bupivacaine was removed from their infusion, with no persistent changes. Patients who had neurological complications with opioids alone were excluded from the study.

In this series, 102 patients had no changes in neurological examination, including sensory function, reflexes, motor function or subjective complaints of numbness. Of these 102 patients, all diagnostic studies, such as MRI (n=48) or EMG/NCS (nerve conduction studies) (n=31), were unchanged over time.

Two patients experienced numbness within the first few weeks of infusion and complained of sensory loss in a nondermatomal fashion. In both of these patients, the bupivacaine was removed and the complaints dissipated over a few days and subsequently resolved. There were no sequelae from this complication. In four patients, significant neurological changes occurred during the course of surveillance. One patient developed a foot drop, another developed marked motor weakness and two patients developed major changes in both sensory and neurological motor function. Upon obtaining further diagnostic studies, one patient was found to have a significant advance in her metastatic disease of the spine unrelated to any infusion drug or system. In the noncancer patients, two showed worsening on MRI of their disc disease, which correlated clinically with their findings, and the other patient had significant findings of scar-enhancing tissue near the previous laminectomy consistent clinically with a post-laminectomy syndrome. There were no abnormalities that were not explained by clinical studies and examinations. These neurological symptoms/changes were determined to be unrelated to the intrathecal infusion.

Another patient who had prostatic carcinoma developed peripheral edema with the addition of bupivacaine to his pump. He previously had morphine with inadequate pain re-
lief but with no peripheral edema. Once the bupivacaine was removed from the infusion system, the peripheral edema resolved.

He had no untoward long-term deficits from this problem. One patient experienced peripheral edema that was not present before the addition of bupivacaine. Again, this complication dissipated in the patient once the bupivacaine was removed and did not return.

The patients had received no other analgesic other than morphine administered at an average daily dose of 8 mg per day intrathecally or hydromorphone administered at an average daily dose of 1.5 mg intrathecally per day [9]. The bupivacaine dose ranged from 2.0 to 25.0 mg with an average intrathecal dose of 10.0 mg per day. Patients were not excluded based on opiates used by multiple routes, although amount of opioids used in each area was analyzed.

Discussion

Failed back surgery syndrome producing pain has become a major health-care issue in the United States. Many of these patients fail oral medications, nerve blocks and re-operation. Metastatic spine pain often fails to respond to oral, transdermal or intravenous opioid infusions. The use of intrathecal drug administration has become an increasingly accepted treatment option for patients who fail to receive appropriate pain reduction from other routes of delivery. The Food and Drug Administration has approved intrathecal morphine for pain treatment. Unfortunately, many patients fail to receive adequate relief when morphine is used as a sole agent [10]. It has become a more common clinical practice to use second-line therapy in these patients who do not receive adequate pain relief or who have intolerable side effects [11].

These methods of treatment beyond morphine include replacement with another opioid, such as hydromorphone or fentanyl, or adding other agents to opioids [11]. The agents added have most commonly included bupivacaine or clonidine [11]. Despite the widespread use of bupivacaine, the literature has not recorded a great deal of experience regarding safety or efficacy when this drug is added to opioids [10]. The results of this retrospective analysis suggest that in this group of patients the addition of intrathecal bupivacaine provides improved pain relief when compared with opioids alone and show no neurological sequelae in prolonged use. The study is limited by its retrospective design and the progression of disease in both the cancer and the noncancer patient over time. The study was also limited in the need for accurate reporting by the patient with regard to office visits, emergency visits and medications taken. Despite these limitations, this analysis is the most extensive experience ever reported with intrathecal bupivacaine. Further prospective analysis is needed to confirm this information, but the results presented here are certainly encouraging.

Another consideration is that patients were included in this analysis only if their visual analog pain score was greater than 6 on two consecutive occasions. This may bias the data in two ways: the data may be biased favorably toward the bupivacaine arm, because of the high initial pain score; or the data may be biased favorably toward the opioid-alone arm, because these patients were more intractable, making it more difficult to improve on the outcome regardless of interventions. Opioid tolerance may have led to the failure to produce pain relief in the opioid-alone arm. Further studies should examine the role of bupivacaine in reducing further opioid tolerance development when given intrathecally. The rate of dose escalation in intrathecal opioid dosing in the opioid-alone group versus the combined group should also be studied prospectively. Other factors to consider in further study analysis include the site of pain and the type of pain. A study of the amount of pain reduction in a group with primarily neuropathic pain compared with pain reduction in a group with primarily nociceptive pain could shed light on the best use of local anesthetics in intrathecal treatment.

Conclusion

Many patients with severe pain related to failed back surgery syndrome or metastatic spine disease require treatment with intrathecal opioids. In patients treated with intrathecal opioids, a subset of patients will not have acceptable pain relief or acceptable satisfaction over time. In this group of patients the addition of intrathecal bupivacaine allows them to be effectively managed. This may improve long-term outcomes in those patients who develop tolerance to intrathecal opioids. In this analysis not only did pain relief improve with the addition of bupivacaine, but a significant improvement was also seen in health-care utilization including doctors visits, emergency room visits, opioid use and use of other medications. Side effects were rare and self-limited with the addition of bupivacaine. There is no evidence that the addition of bupivacaine to the intrathecal opioid infusion caused permanent neurological sequelae in these patients. Prospective randomized studies are needed to further define the safety and efficacy of prolonged intrathecal infusion of bupivacaine and other local anesthetics.

References


170 One Hundred Seventy Years Ago in Spine . . .

R.A. Stafford, in 1832, described the common occurrence of forward stooped posture in adolescent males, which was not remediable by behavioral or postural change and became fixed. The medical world awaited roentgenography and the doctoral thesis of a Danish orthopedist/radiologist, Holger Werfel Scheuermann, who, in 1921, fully documented the disease most commonly called by his name. Scheuermann said it was not possible to know if the kyphosis caused the wedged vertebrae, or if the wedged vertebrae caused the kyphosis. He believed the abnormality was in the growth plates of the vertebral bodies and he named the disease “osteochondritis deformans juvenilis dorsi.”

References

