Use of Intrathecal Bupivacaine in Refractory Chronic Nonmalignant Pain

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ABSTRACT

Objective. To demonstrate the efficacy and safety of the addition of bupivacaine in restoring pain control and improving quality of life and activity level in patients with chronic nonmalignant pain refractory to intrathecal opioids.

Design. Retrospective study.

Setting. Outpatient clinics.

Patients. Seventeen patients with inadequate pain relief while receiving intrathecal opioids alone.

Interventions. The intrathecal opioid dose was held constant at 14.19 mg/day following the addition of bupivacaine. The initial bupivacaine dose was 2.08 mg/day and 4.83 mg/day at final follow up.

Outcome Measures. Pain relief, activity, depression, and quality of life were measured by the Visual Analog Scale (VAS), Oswestry Disability Index (ODI), Beck Depression Inventory (BDI), EuroQol 5D (EQ-5D), and Short Form 36 (SF-36), respectively. Reduction in oral medication use, return to employment, and device-related complications were also analyzed. Outcomes were evaluated prior to pump implantation, before the addition of bupivacaine (baseline), and every 6 months thereafter.

Results. Seventeen patients were followed for 29.60 ± 19.01 months. The average pain reduction measured by the VAS was 32.2%. The ODI improved 19.1%; BDI improved 17.9%; EQ-5D improved by 0.56; and the SF-36 showed statistical improvement in six of eight domains. Mean oral/transdermal opioid use reduced from 49.01 mg/day to 23.02 mg/day and oral non-opioid medications reduced from 2.2 classes to 1.0 class after the addition of bupivacaine. Two additional patients returned to work. No neurological sequelae resulted from adding bupivacaine.

Conclusions. The addition of intrathecal bupivacaine restores pain control, improves activity level, quality of life, and mental health in this patient group.

Key Words. Bupivacaine; Intrathecal; Opioids; Chronic Pain; Safety; Efficacy

Introduction

Intrathecal infusion of opioids has been used successfully as a first-line therapy in the treatment of chronic pain which has proved refractory to conventional medical therapy [1]. The opioids appear to control the nociceptive pain but the neuropathic pain, which is caused by a primary lesion or dysfunction of the nervous system [2], has proven less responsive to the opioid analgesics [3]. Under these circumstances the opioid dose needs to be constantly increased over time as patients experience diminished pain control [4–8].
However, higher opioid dosages lead to an increasing incidence of undesirable side effects. When faced with this dilemma, an admixture of opioids with other drugs such as intrathecal local anesthetics is considered [1,9].

Morphine exercises its effects on pain control by binding to μ, δ, and κ opioid receptors [10,11]. This activates potassium channels resulting in membrane hyperpolarization of postsynaptic neurons originating in the dorsal horn [12–14]. Voltage sensitive calcium channels are inhibited, reducing the release of neurotransmitters from the presynaptic terminals of the small primary afferents [12,13,15–18]. The effects of the opioid receptors are mediated by a G protein [19]. In contrast, bupivacaine, an amino-amide local anesthetic agent, prevents the generation and conduction of nerve impulses by sodium channel blockade [1,20]. Studies have shown that bupivacaine synergistically enhances the effect of the intrathecal opioids when used in combination [1,21–25].

Another benefit of the addition of bupivacaine may be the reduced incidence of intrathecal granuloma formation as a lower intrathecal opioid dose is required for adequate pain relief. It has been shown in the literature that both morphine and hydromorphone are associated with a concentration-dependent risk of catheter-tip granuloma formation [1].

Despite the current body of literature supporting the use of intrathecal bupivacaine as an admixture [1,26], its use continues to be controversial. The efficacy of long-term intrathecally administered opioids used in combination with local anesthetics for the treatment of nonmalignant pain has been fragmentally documented in the literature [9,20,27–33]. As this field evolves, increasing attention is being directed to the compatibility of medications within the drug delivery system and the associated adverse drug effects.

The aim of this study is to demonstrate the efficacy and safety of the addition of intrathecal bupivacaine in patients with chronic nonmalignant pain who have proven refractory to intrathecal opioids used alone.

Methods
Patient Selection
This is a retrospective study. At our institution, we have a database of 84 patients with chronic nonmalignant pain who were being treated with intrathecal opioids. From this database, we identified 23 patients whose pain control had diminished over time after initial improvement (i.e., initially greater than 50% improvement in the Visual Analog Scale (VAS) during the morphine trial but then reverted to less than 30% pain relief) or had developed intolerable opioid-related side effects. In these patients, bupivacaine had been added to the opioid infusion in order to restore effective pain control. The opioid dose had been left unchanged following the addition of bupivacaine. One patient was excluded from the analysis due to an allergy to local anesthetics, 2 patients did not consent to participate in the study, and 3 patients were lost to follow up leaving a group of 17 patients whose results are being presented. Prior to study participation, informed consent was obtained from all patients. This study was approved by the health region’s research ethics board.

All 84 patients in the database had been previously treated and proved refractory to conventional medical management such as pharmacotherapy (oral/transdermal opioids, nonsteroidal anti-inflammatories, tricyclic antidepressants, anticonvulsants, and antispasmodics), physiotherapy, occupational therapy, transcutaneous electrical nerve stimulation, psychotherapy, and complementary medicine. All had undergone psychiatric evaluation prior to initial pump implant, and were found to have no major active psychiatric illness. Of the 17 patients included in this group, 4 patients had been previously treated by implantation of a spinal cord stimulator which subsequently failed to achieve adequate pain relief and the system was removed.

Initially, a trial of intrathecal morphine had been conducted over a varying period lasting 1–2 weeks period using an externalized DuPen catheter (Bard, Salt Lake City, UT) and a Continuous Ambulatory Drug Delivery pump (Deltec, Inc., St. Paul, MN). All patients achieved more than 50% pain relief without side effects, meeting the criteria for implantation of a fully programmable SynchroMed pump (Medtronic, Inc., Minneapolis, MN).

Outcome Measures
We reviewed previously recorded parameters consisting of: 1) pain intensity level evaluated by VAS; 2) activity level evaluated by the Oswestry Disability Index (ODI) [34]; 3) depression evaluated using the Beck Depression Inventory (BDI) [35]; and 4) quality of life assessed using the EuroQol 5D (EQ-5D) [36] and Short Form 36 (SF-36) Health
Survey [37] questionnaires. We also reviewed the intrathecal opioid and bupivacaine dosage history, adverse drug effects and device-related complications, the use of oral medications, and employment status. These evaluations were completed before implantation of the SynchroMed pump, before the addition of intrathecal bupivacaine (baseline), 6 months after the addition of bupivacaine, and every 6 months thereafter. These patients have a minimum follow up of 6 months after the addition of bupivacaine. Medical record reviews and data analysis were conducted by a disinterested third-party, not directly involved in patient care and with a background in pain management.

**Statistical Analysis**

Statistical analysis was conducted using SPSS (SPSS Inc., Chicago, IL). The paired Student’s t-test was used for statistical comparisons. P values less than 0.05 were considered statistically significant.

**Results**

**Patient Demographics**

Patient demographics for this group are summarized in Table 1. The mean age of the study population at last follow up was 53.5 ± 11.2 years. Six patients were male (35%) and 11 patients were female (65%). Five patients presented with neuropathic pain, three with nociceptive pain, and nine with mixed neuropathic-nociceptive pain. The mean duration of pain was 13.2 ± 9.6 years. Eight patients (47%) were Worker’s Compensation cases. The mean length of the opioid-alone phase of intrathecal therapy was 12.02 ± 15.69 months and the mean length of the opioid-bupivacaine phase of intrathecal therapy was 29.60 ± 19.01 months.

**Type of Intrathecal Opioid Infusion Prior to the Addition of Bupivacaine**

Initially, 11 patients were receiving intrathecal morphine and the remaining 6 patients, intrathecal hydromorphone. For the purposes of reporting, we have converted the hydromorphone doses into morphine equivalents (1 mg intrathecal morphine = 0.2 mg intrathecal hydromorphone) [38]. This conversion method was used as it appears to be the most popular method of reporting within the literature and allows for clearer comparison.

The mean initial daily dose of opioids was 1.35 ± 0.90 mg per day. At the time of addition of bupivacaine, the mean daily dose of opioids had been incrementally increased to 14.19 ± 20.79 mg per day, without improving pain control. This dose was held constant after the addition of bupivacaine (Table 2). The dilution of the opioid dose upon the addition of bupivacaine was accounted for by increasing the opioid concentration.

**Intrathecal Bupivacaine Dosages**

The initial mean daily dose of bupivacaine was 2.08 ± 0.64 mg per day and increased to 2.68 ± 1.28 mg per day at 6 months after the addition of bupivacaine. At the last follow up, the mean

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**Table 1** Demographics of the study population

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (Years)</th>
<th>Gender</th>
<th>Syndrome Causing Chronic Pain</th>
<th>Duration of Pain (Years)</th>
<th>Location of Pain</th>
<th>Pain Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>F</td>
<td>C6 radiculopathy</td>
<td>4</td>
<td>Neck/arms</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>Grade IV L5-S1 spondylolisthesis</td>
<td>12</td>
<td>Low back</td>
<td>Mixed</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>F</td>
<td>Facet joint syndrome</td>
<td>33</td>
<td>Low back/legs</td>
<td>Nociceptive</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>F</td>
<td>Small fiber neuropathy</td>
<td>6</td>
<td>Feet</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>Failed back surgery syndrome</td>
<td>25</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>M</td>
<td>Failed back surgery syndrome</td>
<td>8</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>F</td>
<td>Failed back surgery syndrome</td>
<td>17</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>F</td>
<td>Failed back surgery Syndrome</td>
<td>10</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>F</td>
<td>Degenerative disk disease</td>
<td>3</td>
<td>Low back</td>
<td>Nociceptive</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>F</td>
<td>Small fiber neuropathy</td>
<td>8</td>
<td>Feet</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>F</td>
<td>CRPS I secondary to postherpetic neuralgia</td>
<td>5</td>
<td>Legs/feet</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>12</td>
<td>46</td>
<td>M</td>
<td>Failed back surgery syndrome</td>
<td>14</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>F</td>
<td>Failed back surgery syndrome</td>
<td>3</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>14</td>
<td>54</td>
<td>M</td>
<td>Failed back surgery syndrome</td>
<td>19</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>15</td>
<td>49</td>
<td>M</td>
<td>CRPS I due to crush injury to ankles</td>
<td>30</td>
<td>Legs/feet</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>16</td>
<td>68</td>
<td>M</td>
<td>Failed back surgery syndrome</td>
<td>5</td>
<td>Low back/legs</td>
<td>Mixed</td>
</tr>
<tr>
<td>17</td>
<td>43</td>
<td>F</td>
<td>Endometriosis</td>
<td>22</td>
<td>Pelvis</td>
<td>Nociceptive</td>
</tr>
</tbody>
</table>

CRPS = complex regional pain syndrome.
The mean daily dose of bupivacaine was 4.83 ± 2.37 mg per day (Table 2). The mean daily dose escalation of bupivacaine per month was 0.090 ± 0.066 mg per month. Dose escalation was guided by clinical response.

### Pain Control

The mean pain intensity scores as evaluated by the VAS was 90.95 ± 9.18 mm at pump implantation, 88.18 ± 13.26 mm prior to the addition of bupivacaine, 63.30 ± 25.94 mm 6 months after the addition of bupivacaine, and 55.99 ± 25.94 mm at last follow up (29.60 ± 19.01 months) (Figure 1). The improvement in pain scores pre-bupivacaine and 6 months after the addition of bupivacaine was statistically significant ($P = 0.002$) and continued to improve at last follow up ($P = 0.00003$).

### Activity Level

The mean ODI score was 71.5 ± 14.7% prior to implantation, 69.9 ± 15.7% prior to the addition of bupivacaine, 49.5 ± 17.5% 6 months after the addition of bupivacaine, and 50.8 ± 17.5% at last follow up (Figure 2). The improvement in ODI scores pre-bupivacaine and 6 months after the addition of bupivacaine was statistically significant ($P = 0.00004$) and the benefit was maintained at last follow up ($P = 0.0002$).

At baseline, only 1 patient (6%) was employed. At last follow up, 3 patients (18%) were employed (Table 2).

### Depression

The mean BDI score (maximum score of 63) was 25.59 ± 9.55 prior to implantation, 23.06 ± 10.24 prior to the addition of bupivacaine, 10.88 ± 5.59 6 months after the addition of bupivacaine, and 11.77 ± 7.59 at last follow up (Figure 3). The improvement in BDI scores pre-bupivacaine and 6 months after the addition of bupivacaine was statistically significant ($P = 0.001$) and the benefit was maintained at last follow up ($P = 0.001$).

### Quality of Life

EQ-5D scores were calculated using the Health State York Measurement and Valuation of Health

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**Table 2** Additional outcomes (all results reported as mean ± SD)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pump Implantation</th>
<th>Addition of Bupivacaine (Baseline)</th>
<th>6 Months Post-Bupivacaine</th>
<th>Final Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathecal opioid dose† (mg/day)</td>
<td>1.35 ± 0.90</td>
<td>14.19 ± 20.79</td>
<td>14.19 ± 20.79</td>
<td>14.19 ± 20.79</td>
</tr>
<tr>
<td>Intrathecal bupivacaine dose (mg/day)</td>
<td>—</td>
<td>2.08 ± 0.64</td>
<td>2.68 ± 1.28</td>
<td>4.83 ± 2.37</td>
</tr>
<tr>
<td>Oral/transdermal opioid medications† (mg/day)</td>
<td>49.01 ± 28.89</td>
<td>Data missing.</td>
<td>Data missing.</td>
<td>23.02 ± 20.11†</td>
</tr>
<tr>
<td>Oral non-opioid medications (number of classes‡)</td>
<td>2.2 ± 1.2</td>
<td>Data missing.</td>
<td>Data missing.</td>
<td>1.0 ± 1.2‡</td>
</tr>
<tr>
<td>Employment status (number of patients)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

† Opioid doses (intrathecal and oral/transdermal) are reported in morphine equivalents.
‡ Non-opioid medications were categorized using five classes: anticonvulsants, antispasmodics, nonsteroidal antiinflammatories, COX-2 inhibitors, and antidepressants.
§ Reduction in opioid ($P = 0.04$) and non-opioid medications ($P = 0.004$) are statistically significant. At final follow up, 3 patients were able to manage their pain with intrathecal drugs only and without the use of oral medications.
Time Trade-Off Approach (−0.594 = worst possible health state, 1.000 = best possible health state) [39]. The mean EQ-5D score was −0.14 ± 0.22 prior to implantation, −0.04 ± 0.34 prior to the addition of bupivacaine, 0.49 ± 0.34 6 months after the addition of bupivacaine, and 0.52 ± 0.36 at last follow up (Figure 4). The improvement in EQ-5D scores pre-bupivacaine and 6 months after the addition of bupivacaine was statistically significant ($P = 0.0005$) and continued to improve at last follow up ($P = 0.00003$).

The SF-36 scores showed the most improvement in the body pain and vitality scales. The difference between SF-36 scores pre-bupivacaine and 6 months after the addition of bupivacaine was statistically significant ($P < 0.05$) except for role-physical. The difference between SF-36 scores pre-bupivacaine and at final follow up is statistically significant in all domains ($P < 0.05$) except for role-physical and general health (Figure 5).

**Relationship between the Etiology of Pain and the Benefits of the Addition of Bupivacaine**

Patients with a neuropathic component to their pain (pure neuropathic or mixed pain, $N = 14$) experienced greater benefit in all outcomes compared with patients with pure nociceptive pain ($N = 3$). These results are summarized in Table 3.

**Oral Medication Use (Doses Are Reported in Parenteral Morphine Equivalents)**

Prior to implantation, 16 patients were taking oral medications. At final follow up, 3 patients were...
able to manage their pain with intrathecal drugs only and without the use of oral medications.

Prior to implantation, the mean daily dose of oral/transdermal opioid medications was 49.01 ± 28.89 mg. After the addition of bupivacaine, the dose reduced to 23.02 ± 20.11 mg ($P = 0.04$, Table 2). Thirteen patients (76%) either reduced their use of or completely abstained from using

**Table 3** Benefits of the addition of bupivacaine by pain etiology (final follow up)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Neuropathic Group (N = 5)</th>
<th>Mixed Group (N = 9)</th>
<th>Nociceptive Group (N = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief—VAS (%)</td>
<td>48.7</td>
<td>27.1</td>
<td>20.0</td>
</tr>
<tr>
<td>Functional improvement—ODI (%)</td>
<td>26.8</td>
<td>16.8</td>
<td>13.3</td>
</tr>
<tr>
<td>Mental health improvement—BDI (%)</td>
<td>36.5</td>
<td>11.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Quality of life improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>0.70</td>
<td>0.55</td>
<td>0.34</td>
</tr>
<tr>
<td>SF-36 (total score) (%)</td>
<td>34.4</td>
<td>16.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Number of patients returning to work</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

VAS = Visual Analog Scale; ODI = Oswestry Disability Index; BDI = Beck Depression Inventory; EQ-5D = EuroQol 5D; SF-36 = Short Form 36.
oral/transdermal opioid medications at final follow up. The decision to reduce oral medications was a collaborative effort by the patient and physician. It was guided by the improvement in pain control as reported by the patient.

Non-opioid medications were categorized using five classes: anticonvulsants, antispasmodics, nonsteroidal anti-inflammatories, cyclooxygenase-2 (COX-2) inhibitors, and antidepressants. Prior to implantation, the average number of classes of oral non-opioid medications being taken by the patients was $2.2 \pm 1.2$ and $1.0 \pm 1.2$ after the addition of bupivacaine ($P = 0.004$, Table 2).

These results show that there is a significant reduction in the use of oral/transdermal opioid ($P = 0.04$) and non-opioid ($P = 0.004$) medications after the introduction of bupivacaine.

**Drug-Related Side Effects and Hardware Complications**

The most common side effects related to the intrathecal opioids experienced by our patient population were gastrointestinal upset, loss of appetite, and night sweats. These side effects are similar to what is described in the literature [38]. Side effects were managed by a reduction in the daily opioid dose.

The introduction of bupivacaine to the opioid infusion caused no significant neurological sequelae except in one patient, who experienced mild weakness and paresthesias in the lower limbs in a nondermatomal fashion. This was corrected by a reduction in the daily dose of bupivacaine.

In this series, 13 patients reported 19 different device-related complications. Catheter-related complications included fractures, disconnections, obstructions, kinks, and nerve root irritation (N = 9). Pump-related complications included pump rotation (N = 3) and pump-pocket seroma (N = 5). Infectious complications included superficial wound infection (N = 2) which resolved with antibiotics. Surgical intervention was required for all cases of catheter-related complications and pump rotation problems. None of these patients required explantation of the system.

**Discussion**

Morphine is approved as a first-line agent for intrathecal drug therapy of refractory chronic pain [1,26]. However, the combination of agents for intrathecal therapy is an important treatment option when inadequate pain relief is achieved with intrathecal monotherapy, especially in patients with neuropathic pain [1,9]. Many pain states have multiple underlying mechanisms and consequently a drug with a defined mechanism of action may be effective against only one or two components, but often not all. Therefore, a combination of agents may act on multiple components producing a synergistic action to control the pain [38]. Intrathecal opioids target the opioid receptors in the spinal cord while intrathecal bupivacaine acts on the nerve roots and the dorsal root entry zone level, enhancing the pain control [9,38]. Bupivacaine facilitates this by reversibly blocking sodium channels, thus preventing the transmission of pain signals via the Aδ and C fibers [1,20].

Bupivacaine may also synergistically enhance the analgesic effect of opioids by: 1) inhibiting voltage-sensitive calcium channels thereby enhancing the opioid-induced presynaptic inhibition of neurotransmitter release from the Aδ and C fiber terminals [1,22,23] and 2) inducing a conformational change in the spinal opioid receptors (μ, δ, and κ receptors) [25].

The stability of bupivacaine alone or in combination with morphine in intrathecal pumps has been previously established. Bupivacaine retains concentrations of greater than 96% of the original value after incubation at 37°C in an implanted pump delivery system for approximately 3 months [40,41]. Therefore, the combined use of morphine and bupivacaine does not require any change in the scheduling of pump refills.

Our data demonstrates that the use of intrathecal bupivacaine in combination with opioids appears to be safe with adverse effects being mild in severity and rare in occurrence. The side effects reported in this study are similar to what has been described in the literature [38]. System complications are inherent to the present state of technology of the pump and the catheters that are used along with it [38].

Baseline EQ-5D and SF-36 scores suggest that the quality of life was extremely poor in this group of patients. Twelve patients (71%) considered their quality of life to be worse than death (i.e., a negative EQ-5D score). Such low quality of life scores are reported in patients with chronic heart disease and cancer pain [42]. The addition of bupivacaine improved the quality of life by 0.56 (EQ-5D) and in six of eight domains (SF-36), improved their functional level by 19.1% (ODI), and improved pain scores by 32%. This is reflected in the fact that prior to treatment, only one patient was employed as compared with three patients after treatment.
Another factor that may contribute to the reduced employment rate at baseline may be the continued use of oral opioids in this patient population. Our study revealed that 76% of the total population either reduced their use of or completely abstained from using oral opioid medications at final follow up. These issues become very important, as research has shown that patients off work for more than 3 years are unlikely to return to gainful employment [43,44].

A double-blind, randomized, crossover, multicenter study conducted by Mironer et al. [9] shows no improvement in pain control with the addition of different concentrations of bupivacaine (4, 6, or 8 mg per day) to the intrathecal opioid infusion. This may have been due to the short treatment period with each bupivacaine-opioid admixture (1 month) and the inadequate number of patients to assess whether the order in which treatments were given had an effect on the results. In contrast, our study and those of Krames et al. [20] and Deer et al. [30], while retrospective studies, showed a clinically significant improvement. Krames et al. [20] found that adding bupivacaine improved analgesia and reduced side effects in patients with neuropathic pain. Deer et al. [30] similarly found that VAS score improved by 32% compared with intrathecal morphine alone.

The duration of the opioid-alone phase of therapy may have also contributed to the difference in outcomes. The opioid-alone phase lasted 27 months in Mironer’s study vs 12 and 17 months in our study and Krames’ study, respectively. Deer’s study did not clearly discuss this parameter. A longer opioid-alone phase may result in a patient’s pain becoming more resistant to the addition of bupivacaine and possibly progression of the underlying disease. A third possibility is that the longer the pain persists without adequate pain control, the more likely changes may occur in the prefrontal cortex. These changes make it difficult to achieve adequate pain control despite proper therapy later on. This may explain why Mironer’s study population failed to achieve adequate pain relief with the addition of bupivacaine.

Nitescu et al. [33] conducted a study of 90 patients. In their report, 95% of patients achieved acceptable (60–100%) pain relief in the short term (median 60 days), but in the long term (median 206 days), the failure rate was 34%. This is due to the fact that 93% of the failure group had psychiatric and personality disorders causing non-compliance in their study group.

Our results indicate a higher benefit ratio in pain control and improvement in quality of life in patients suffering from neuropathic or mixed pain as compared with those with nociceptive pain. This is consistent with the literature [20]. The diagnosis of the neuropathic nature of the pain was established by a clinical history of nerve injury with resultant radiation of pain in a dermatomal pattern and neurologic deficit. This was confirmed by clinical examination of sensory/motor/reflex changes and supporting tests such as X-ray, magnetic resonance imaging, and electromyography. However, these results should be interpreted with caution because of the small number of patients in the nociceptive pain group.

In patients with inadequate pain control with intrathecal opioids alone, the tendency is to gradually increase the dose of opioids to optimize pain control, but the disadvantage of this practice is that the incidence of intolerable side effects increases. In such cases, the necessity of using a second agent arises. In this study, we have introduced bupivacaine when the mean daily dose of opioids reached 14.19 mg at which time the dose was held constant. In our study, the mean daily dose of bupivacaine to alleviate the pain was 4.83 mg. Titration of the bupivacaine dose may have been required to manage the gradual reduction in the efficacy of the opioids, increasing patient activity level, or disease progression. In the literature, the recommended daily dose of intrathecal bupivacaine to achieve pain control is 2–25 mg per day [26]. Because we were able to achieve pain relief with a dose of bupivacaine in the low range, this may be a reflection of the synergistic action of opioids and bupivacaine. In other words, bupivacaine seems to delay or slow the development of opioid tolerance.

In our patients with complex regional pain syndrome, the addition of bupivacaine did not prevent the spread of the disease from one limb to the other or the associated allodynia. The spread of the disease was genuine and was confirmed by clinical presentation. These patients had undergone psychiatric evaluation prior to their inclusion in the study and received ongoing psychiatric support. This is consistent with the literature [31,33].

As far as we are aware, this is the only study to report standardized, quantitative measurements of the change in depression, quality of life, and activity level using the combination of intrathecal bupivacaine and opioids for the treatment of chronic nonmalignant pain. Other strengths of this study include the long follow up (29.60 ± 19.01 months), a group of patients with a long history of
chronic pain (mean duration 13.2 ± 9.6 years), and that these patients were refractory to intrathecal opioids alone and conventional medical management. Limitations of this study include its retrospective nature and small study population.

Conclusion

This study suggests that in a select group of patients who have proven refractory to the use of intrathecal opioids alone and conventional management, the addition of intrathecal bupivacaine restores pain control, improves activity level and quality of life, and reduces depression. The use of intrathecal bupivacaine is safe and well tolerated. Large-scale, prospective, randomized studies are required to further evaluate the benefits and safety of intrathecal bupivacaine.

References


37 McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey: II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31: 247–63.


