Original Research Article

Combination of Intrathecal Opioids with Bupivacaine Attenuates Opioid Dose Escalation in Chronic Noncancer Pain Patients

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Abstract

Objective. The purpose of this study was to examine the effect of intrathecal (IT) coadministration of bupivacaine with opioids during the initial phase of opioid titration and up to 1 year after implantation of an IT drug delivery system (IDDS).

Design. The study was designed as a retrospective study.

Outcomes Analyzed. The outcomes analyzed for this study were pain relief, oral opioid consumption, IT opioid, and bupivacaine dosage.

Methods and Patient Population. The patient population for this study were consecutively implanted patients over a period of 6 years in a tertiary single center with multiple practitioners. In this retrospective study, 126 consecutive noncancer intractable pain patients were implanted with IDDS and initiated with an IT opioid (O) as a single medication or an IT opioid and bupivacaine (O + B). Pain intensity, amount of oral opioids, dose, rate, and concentration of IT opioids and bupivacaine, and number and type of IT medication used were recorded at preimplant, implant, and at 3, 6, and 12 months postimplant.

Intervention. The intervention used for the study was the IT delivery device implant.

Results. Significant reduction in pain intensity was observed in both groups at 12 months postimplant (O group: baseline 7.42 ± 2.1 to 5.85 ± 2.8 [n = 72, P < 0.001]; O + B group 7.35 ± 2 to 5.03 ± 2.4 (n = 54; P < 0.001)). The combination of opioids with bupivacaine from the start of IT infusion treatment resulted in a reduced progression of opioid dose escalation in comparison to patients started with opioids (O group). The rate of increase of IT opioids in the O group at 12 months was 535 ± 180%, whereas in the O + B, the dose increase was significantly lower at 185 ± 85% (P < 0.004). In both groups, there was a statistically significant decrease in oral opioid consumption compared with preimplant doses.

Conclusion. Concomitant initial coadministration of IT bupivacaine with opioids blunts the rate of IT opioid dose escalation during the first year after implant of an IDDS. More studies are necessary to thoroughly examine IT opioid dose escalation and the effects of addition of bupivacaine to IT opioids. Blunting IT opioid dose escalation may be a beneficial long-term effect of IT bupivacaine.

Key Words. Intrathecal; Local Anesthetics; Bupivacaine; Opioids; Postlaminectomy Syndrome; Chronic Low Back Pain
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Introduction

Intrathecal drug delivery (IDD) is an important intervention in the management of refractory cancer- and noncancer-related chronic pain [1,2]. The intrathecal (IT) route for medication administration bypasses the blood barrier and results in higher drug concentration in close proximity to the target receptors [3]. Opioids, including morphine and hydromorphone, are the most commonly used IT analgesic medications [4]. Despite improved delivery and effectiveness with the IT route [5], opioid side effects still occur, including the development of tolerance [6–9]. Tolerance refers to increased medication dosage requirement to maintain analgesic efficacy. Tolerance to opioids appears to occur with oral and IT opioids and may be age dependent, with younger patients displaying more robust tolerance than older patients [9,10]. It may also be more problematic in noncancer-related pain given limited survival of cancer patients [11]. Of concern, high doses/concentrations of IT morphine or hydromorphone have been associated with the development of IT granulomas [12]. These are sterile growths of macrophages, neutrophils, and monocytes typically occurring at the tip of IT catheters and are adherent to the dura and sometimes the cord. IT granulomas occur in about 3% of patients implanted with IT pumps for pain and may result in neurologic compromise [13]. Opioid-induced hyperalgesia occurs with higher doses of opioid therapy, including the IT route [14]. Given the complex nature of the pain-signaling process, other IT analgesic medications are often coadministered with opioids to improve pain control, including the local anesthetic bupivacaine [15]. Administered spinally, local anesthetics are synergistic with opioids as shown in animal studies [16,17] and acute clinical pain studies [18,19]. However, that effect has not been born out in studies on the effectiveness of bupivacaine in chronic pain patients receiving IT analgesia. The purpose of this study was to explore the effect of bupivacaine added to IT opioids, over a 12-month period after IDD initiation, in a large group of patients with chronic noncancer pain.

Methods

Study Population

Following Institutional Review Board approval, a retrospective analysis was conducted of patients consecutively implanted with IDD systems (IDDS) at the Cleveland Clinic Foundation by various practitioners in the Department of Pain Management between 2000 and 2006. From this database, two cohorts of patients were analyzed based on the initial medications used intrathecally:

1 IT opioids (comprised of morphine or hydromorphone); “O” cohort.
2 IT opioids (morphine or hydromorphone) and bupivacaine; “O + B” cohort.

This study is a primary analysis of the data collected during the first year postimplant. The decision to start IT treatment with dual medications was based upon individual practitioner’s preferences and judgment based on the clinical condition and perceived usefulness of added local anesthetic. The database reviewed contains a total of 171 consecutively implanted patients. Prior to implantation, a stepwise multidisciplinary approach was applied in the treatment of these patients including appropriate psychological assessment, physical and occupational therapy as indicated, and conservative medical management including medication and minimally invasive interventions. To be included in the study, patients had to be implanted with IT pumps for the delivery of opioids for the management of intractable noncancer pain. All patients had a successful IT trial using a continuous IT infusion in an in-patient setting prior to being implanted with the pump system. Patients achieving over 50% pain relief, without side effects, met the criteria for implantation of a SynchroMed pump (Medtronic, Inc., Minneapolis, MN, USA).

The medications used intrathecally were morphine sulfate and hydromorphone either as single medications or combined with the local anesthetic bupivacaine or the alpha-2 adrenergic agonist, clonidine (the clonidine combination was excluded from this study). Exclusion criteria included: cancer pain, IT baclofen for spasticity, and other IT medications used as a monotherapy or combination therapy (such as local anesthetics alone or ziconotide) in the absence of IT opioids.

Patients were followed up for 1 year postimplant and various data parameters were collected including: age, sex, indication, pain scores using a numerical rating scale (NRS; 0 = no pain and 10 = worse imaginable pain), oral opioids intake before and after implant, IT opioid dose, and IT medications type and rate. Charts were reviewed for pain intensity scores (using the NRS) from before the IT pump trial as well as at 3, 6, and 12 months postimplant. Similarly, oral opioid consumption was recorded at baseline (trial date) and at 3, 6 and 12 months postimplant and is expressed in morphine equivalent daily dose (MEDD). IT opioids used in the selected patient population included morphine or hydromorphone. Oral and IT opioid doses used were converted to morphine sulfate equivalent doses using accepted conversion ratios (morphine:hydromorphone to 5:1) [20].

\[
\Delta \text{(in %)} = \frac{\text{[current dose} - \text{baseline dose (at implant)]}}{\text{baseline opioids dose}} \times 100
\]

The latter approach reflects changes in the rate of increase from baseline rather than comparing the various absolute doses, which may vary significantly from patient to patient. To compare oral opioids consumption over the first year postimplant, the average MEDD in mg was compared from implant time (time 0) to 3, 6, and 12 months.
postimplant. An intent-to-treat analysis was used based on initial treatment allocation of opioids alone or opioids + bupivacaine. Patients who have had bupivacaine added to opioids in their pumps at later stages than the initial implant time were included in the O group.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA). The difference in pain scores, opioid dose (MEDD), and concentration between baseline (month 0) and each follow-up time point (i.e., month 3, 6, and 12) was examined by a paired \( t \)-test. The difference in dose and drug concentration between two cohorts was compared using Kruskal–Wallis test within each cohort. The data were summarized by mean and standard deviation of the mean (SD), and in chart presentation as mean and standard error of the mean. All tests were two-sided, and \( P \)-values less than 0.05 were considered statistically significant.

Results

Description of the Patient Population

Two cohorts of patients were isolated from a total of 171 patients; all implanted consecutively with IDDS. Forty-five patients were excluded from our study analysis because: 1) their indication for implant was cancer-related pain (13 patients); 2) they were treated only with baclofen infusion for spasticity (12 patients); 3) their infused medication(s) did not include opioids (11 patients); and 4) initial infused opioid was not morphine or hydromorphone or a combination that did not contain local anesthetics (9 patients). The remaining 126 patients were included in the study. Patient demographics, including age, sex, indication for implant, average pain score at implant, and oral opioid consumption at the time of implant are shown in Table 1. There were 72 patients who were initiated on an opioid intrathecally (morphine or hydromorphone; O group) as a single medication treatment and 54 patients who were initiated with a combination of an opioid (morphine or hydromorphone) and local anesthetic (bupivacaine; O + B group). In the O group, the average patient age was 57.6 ± 12.9 years old; 39 (54%) were males and 33 (46%) were females. In the O + B group, the average patient age was 56.6 ± 16.2 years old; 33 (61%) were males and 21 (39%) were females. In the O cohort: 42 patients had an indication of failed back surgery syndrome (FBSS), 5 patients had complex regional pain syndrome (CRPS), 6 patients had spinal cord pathology, 3 had visceral pain, and 16 patients had various types of pain, including postherpetic neuropathy, lumbosacral neuitis, diabetic peripheral neuropathy, and vertebral fracture due to severe osteoporosis. From the O + B cohort, 27 implanted patients had an indication of FBSS, 5 patients had CRPS, 3 patients had spinal cord pathology, 4 had visceral pain, and 15 patients had various types of chronic and neuropathic pain. The IT therapy time frame analyzed was the initial 12 months postimplant.

Table 1  Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>IT O Cohort</th>
<th>IT O + B Cohort</th>
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<tbody>
<tr>
<td>N = 72 (%)</td>
<td>N = 54 (%)</td>
<td></td>
</tr>
<tr>
<td>Age mean ± SD</td>
<td>57.6 ± 12.9</td>
<td>56.6 ± 16.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (54)</td>
<td>33 (61)</td>
</tr>
<tr>
<td>Female</td>
<td>33 (46)</td>
<td>21 (39)</td>
</tr>
<tr>
<td>NRS score (at implant)</td>
<td>7.42 ± 2.1</td>
<td>7.35 ± 2</td>
</tr>
<tr>
<td>Indication for implant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed back surgery</td>
<td>42 (59)</td>
<td>27 (50)</td>
</tr>
<tr>
<td>CRPS</td>
<td>5 (7)</td>
<td>5 (9.2)</td>
</tr>
<tr>
<td>Spinal cord pathology</td>
<td>6 (8)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Visceral pain</td>
<td>3 (4)</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Other (including postherpetic neuropathy, lumbosacral neuitis, diabetic peripheral neuropathy)</td>
<td>16 (22)</td>
<td>15 (27.8)</td>
</tr>
<tr>
<td>Oral opioid dose at time of implant (in mean ± SD mg/day)</td>
<td>138 ± 112</td>
<td>126 ± 87 mg</td>
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</table>

SD = standard deviation; NRS = numerical rating scale; CRPS = complex regional pain syndrome; IT O = intrathecal opioid; IT O + B = intrathecal opioid + bupivacaine.

Intrathecal Combination Therapy

Medications Used Intrathecally During the Initial 12 Months Postimplant

From the 126 patients included, 72 patients had initial IT opioids (IT O), morphine (ITm), or hydromorphone (ITh) as single medications and 54 had a combination of IT O with bupivacaine (ITb) (Table 2). During the first year postimplant, there were modifications in the medications used. In particular, this was seen in many patients of the IT O cohort, where bupivacaine was added either at 3, 6, or 12 months. Regardless, an intent-to-treat analysis was
performed and patient data were analyzed based on the initial assigned treatment group.

At the initiation of IDD, from the 72 patients in the IT O cohort, 59 were receiving ITm and 13 ITh (Table 2). At 3 months postimplant (looking at the same group), 52 patients were receiving ITm, 14 ITh, 18 IT opioid and bupivacaine, and 2 patients >2 medications; while at 12 months, 38 patients were receiving morphine, 8 hydromorphone, 22 O + B (15 m + b and 7 h + b), and 2 patients ended up with >2 medications (commonly added medication included clonidine or ziconotide). Among the O + B cohort (Table 2), from 54 patients 42 were started on IT m + b and 12 on IT h + b. At 12 months, 4 patients ended up on IT m alone, 29 patients ended up on m + b, 12 patients on h + b, and 9 patients on >2 medication with the addition being either clonidine or ziconotide). The decision to add IT medications was made by the physician managing the IT pump, based on the responsiveness of the patient to the IT therapy. Initial IT O dose at implant for the O cohort was 1.83 ± 0.1.7 mg/day (mean ± SD) morphine equivalent (hydromorphone-to-morphine conversion ratio used is 1:5). The starting IT O dose for the O + B cohort was 2 ± 2.01 mg/day morphine equivalent and IT dose of bupivacaine was 6 ± 2.3 mg/day (mean ± SD).

### Pain Relief from IT Therapy During the Initial 12 Months Postimplant

The mean baseline pain intensity score as evaluated by the NRS was 7.42 ± 2.1 for the IT O group at pump implantation and decreased significantly to 5.85 ± 2.8 at 12 months postimplant (P < 0.001). The IT O + B group baseline pain intensity was not different than IT O group at implant and averaged 7.35 ± 2.1 on the NRS. At 12 months, the IT O + B group NRS scores decreased significantly to 5.03 ± 2.4 (P < 0.001) in relation to baseline; however, the ΔNRS was not significantly different from that of the IT O group ΔNRS (P = 0.09). The time-dependent changes in pain intensity scores are depicted in Figure 1.

A responder analysis, similar to that described by Atli et al. [7], was performed to determine the proportion of patients who achieved either 30% or greater, or a 50% or greater pain relief relative to baseline levels, based on the NRS, for each of the groups (Figure 2). At 3 months postimplant, in

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**Table 2** Agents used intrathecally by implanted drug device in patients with chronic noncancer

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time (months)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>0 (Implant)</td>
<td>3</td>
<td>6</td>
<td>12 (Postimplant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I: IT O</td>
<td>72 (O)</td>
<td>66 (O)</td>
<td>52 (O)</td>
<td>46 (O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (O + B)</td>
<td>18 (O + B)</td>
<td>22 (O + B)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (&gt;2 agents)</td>
<td>4 (&gt;2 agents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II: IT O + B</td>
<td>54 (O + B)</td>
<td>51 (O + B)</td>
<td>47 (O + B)</td>
<td>41 (O + B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (O)</td>
<td>4 (&lt;2 agents)</td>
<td>9 (&gt;2 agents)</td>
<td></td>
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</tr>
</tbody>
</table>

Note the addition of bupivacaine in patients started on single opioid agents.

IT O = intrathecal opioid; IT O + B = intrathecal opioid + bupivacaine.

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**Figure 1** Pain response using the visual analog scale (VAS) vs time since implant in months (m) in intrathecal (IT) opioid (IT O) group and IT opioid + bupivacaine (IT O + B) group. Data are presented as mean (line in the box) ± standard deviation. *Denotes significant difference from time 0 in IT O and IT O + B patient groups, respectively.
the O cohort, 28 patients (38%) reported >30% reduction in their NRS scores relative to baseline. At 12 months postimplant, 31% of the patients reported >30% pain relief (Figure 2A). A steady trend was observed in patients with >50% pain relief: 16% at 3 months, and 14.5% at 6 months, and 16% at 12 months. On the other hand, in the O + B cohort at the time of initial refill, 41% of the patients had >30% pain relief and 51% by 12 months postimplant. Similarly, >50% reduction in NRS scores relative to baseline occurred in 18% of patients in the O + B cohort at the time of the first refill and an increasing trend was observed to 27% at 12 months postimplant (Figure 2B).

**Oral Opioid Consumption**

Almost all patients were on an oral opioid regimen before the IDDS implant. Oral opioids were tapered off and weaned gradually based on reported pain control by the patient. The average daily dose of oral morphine (MEDD) was 138 ± 112 and 126 ± 87 mg/day (mean ± SD) in the IT O and IT O + B cohorts, respectively. Supplemental oral opioid doses in the IT O cohort showed a clear decrease from a baseline MEDD value to postimplant values of 100 ± 173 mg (95% confidence interval [CI], 58–142) at 3 months, 81 ± 104 mg (98% CI, 55–105) at 6 months, and 64 ± 93 (95% CI, 39–84) at 12 months (one-way analysis of variance [ANOVA], P < 0.001). The average MEDD in the IT O + B cohort at 3, 6, and 12 months postimplant also declined significantly (126 ± 87 mg/day [95% CI, 102–149], 108 ± 124 mg/day [95% CI, 74–142], and 72 ± 102 mg/day [95% CI 44–99], respectively; one way ANOVA P = 0.001). Oral opioid dose decrease over preimplant dose at 12 months was not significantly different between the two cohorts (IT O cohort 54% average reduction [54 ± 49% n = 72]; IT O + B cohort 44% [44 ± 42%; n = 54; two tailed P = 0.18]). Figures 3A and B demonstrate changes from baseline in IT O and IT O + B cohorts of patients through the first 12 months postimplant.

**IT O+ B Dose Adjustment**

IT medication doses were titrated over the first year postimplant to achieve optimal pain control, while limiting side effects. There were no significant differences in the starting mean values of the initial IT O dose administered between the two groups (1.83 ± 1.7 mg/day and 2 ± 2.01 mg/day for the IT O and IT O + B, respectively, unpaired t-test two-tailed P value is 0.61). The rate of increase in IT O dosage during the first 12 months after implant was determined using changes in percentage of the IT daily opioid dose compared with baseline (implant, time 0). The IT O doses were converted to morphine equivalents using acceptable conversion ratios as described in the Methods. As demonstrated in Figure 4, IT opioid doses increased compared with the initial starting dose in the IT O cohort by 275 ± 160%, 425 ± 175%, and 535 ± 180% at 3, 6, and 12 months, respectively, from the time of implant. Within IT O cohort, the dose increase was significantly different at all time points 3, 6, and 12 months (P < 0.001, n = 72, one-way ANOVA). Similarly, for the IT O + B cohort, an increase of 94 ± 82%, 154 ± 75%, and 179 ± 87% was observed at 3, 6, and 12 months, respectively (P < 0.01, n = 54) as demonstrated on Figure 4. However, when comparing the rate of IT opioid dose increase between the IT O and IT O + B cohorts, a significantly lower rate of IT opioid increase was noted in the IT O + B cohort (independent t-test P < 0.001) at 6 and 12 months. Linear regression lines were fit using the means of IT O in both groups. The $r^2$ values were 0.95 and 0.96 for IT O and IT O + B, respectively. As demonstrated in Figure 5 comparison of linear regression slopes between the two groups reveals significantly different slopes (ANOVA P < 0.05).

**IT Bupivacaine Adjustment**

Fifty-eight patients were initiated using an IT medication mixture of bupivacaine along with either morphine or hydromorphone. This decision was made independently by the attending physician on a patient by patient basis according to physician preferences, patient’s comorbidities and perceived benefits of added bupivacaine. The initial mean daily dose of bupivacaine was 6 ± 2.3 mg per day (95% CI 5.3–6.6 mg). At 12 months postimplant, the mean daily dose of bupivacaine was 9.8 ± 5.3 mg per day (95% CI 8.4–11.3 mg) (Figure 5). This was a 61% increase over baseline starting dose (unpaired two
tailed t-test \( P < 0.001 \). Bupivacaine dose escalation was guided primarily by the response to treatment and was often titrated concomitantly with opioid dose titration in this patient group, given a single-chamber reservoir for the IDDS.

Discussion

The purpose of this retrospective analysis was to determine the effect of bupivacaine coadministration with IT Os in patients with chronic noncancer pain implanted with IDDS. A number of studies have shown that IT opioid

Figure 3 Changes in oral opioid consumption. The dose of oral opioids at 12 months following intrathecal drug delivery system implant is expressed as mean \pm standard error in both groups. *Significant change from baseline. IT = intrathecal.

Figure 4 Bupivacaine intrathecal dose change rate during the first 12 months postimplant. IT = intrathecal.

Figure 5 Intrathecal (IT) dose escalation rate during the first 12 months postimplant in IT opioids vs IT opioid + bupivacaine. A significant difference in escalation rate was observed at 6 and 12 months. Each data point represents the percentage change over the baseline (\( \Delta \) in % as mean \pm standard deviation).
significantly less pronounced opioid escalation was found in both opioid and opioid/bupivacaine group; however, a significantly less pronounced opioid escalation was found in the O + B group compared with the O cohort. Our study demonstrates that the two cohorts analyzed from consecutively implanted patients are similar in their composition and that the difference in opioids escalation is likely due to bupivacaine coadministration with opioids at the time of initiation of IT therapy. This effect may be even more pronounced taking into account that intent-to-treat analysis was used and nearly 34% of the O group patients did end up receiving a combination treatment at 12 months postimplant. The overall improvement in analgesia noted in this report is congruent with previous studies on the effectiveness of opioid IT therapy [8,9,23,25–27]. The effectiveness of IT O vs IT O + B is similar as both treatments appear to provide similar pain relief (as evidenced by similar reduction in NRS scores) as well as similar significant reductions in supplemental oral opioids. There is a trend for an increased proportion of patients maintaining >30% and >50% pain relief in the O + B group; however, this study was not sufficiently powered to conclusively show that effect.

Implantable IT pumps have a significant place in the treatment of chronic noncancer pain refractory to more conservative therapy. Morphine is still the first-line medication for IT delivery; however, other medications are used as standard of care based on clinical judgment and pain characteristics [15]. IT Os target the opioid receptors in the pre- and postsynaptic terminals in the superficial layers of the dorsal horn of the spinal cord and result in suppression of substance P and CGRP release presynaptically and induce hyperpolarization postsynaptically. On the other hand, IT bupivacaine may act preferentially on the nerve rootlets at the dorsal root entry zone level by reversibly blocking sodium channels, thus preventing the transmission of pain signals via the Aδ and C fibers. The primary mechanism of local anesthetic action is a blockade of sodium channels and inhibition of cell depolarization. While the prevailing assumption is that bupivacaine acts only at the DREZ, effects on the dorsal horn can not be excluded [28]. The mechanism and site(s) of opioid–local anesthetic interaction for synergy in pain relief have yet to be elucidated. Potential cellular sites include: 1) changes in opioid pharmacokinetics [17,29]; 2) potentiation of inhibitory effect on neurotransmitter release via modulation of second messenger system such as adenylate cyclase [16,30]; or 3) action on voltage sensitive calcium channels [31].

The pathophysiology of chronic pain is complex and multifactorial. Hence, combination IT therapy is often advocated and practiced by interventional pain physicians. A number of implanting physicians with different medication usage preferences contributed patients to this study. This factor, along with the retrospective nature of the study, makes it impossible to identify determining factors in the choice of IT medications. The combination of IT Os with local anesthetics is common practice and has been proven safe and stable in IT pumps [32,33]. The stability of a commercially available, IT formulation of bupivacaine HCl, and compatibility with the SynchroMed (Medtronic Inc.) infusion system was shown by Deer et al. [33]. Bupivacaine concentration remained greater than 96% of initial concentration after chronic exposure to the intact pump–catheter systems or device materials maintained at 37°C for 12 weeks. Moreover, the mechanical integrity and functional properties of the device materials in contact with bupivacaine were maintained. Furthermore, combinations of morphine sulfate with bupivacaine at 4°C or 23°C for 60 days resulted in potency of morphine nearly 97% and potency of bupivacaine in all samples was 95%. The adverse effects resulting from addition of bupivacaine include numbness, paresthesia and weakness, bowel and bladder dysfunction, and rarely, hypotension, all of which are reversible by decreasing the dose of bupivacaine. The common bupivacaine doses in clinical practice generally range from 2.5 to 30 mg/day [15,20]. In our study, the average starting dose was 6 mg and at 12 months postimplant, the bupivacaine dose was 9.8 mg/day.

To our knowledge, this is the first study demonstrating that bupivacaine addition to opioids from the onset of IT infusion therapy results in blunting of opioid dose escalation in patients with refractory chronic noncancer pain. Several open label studies, prospective and retrospective, have been published over the last decade on the effectiveness of the combination of morphine with bupivacaine [1,32,34–37]. A recent study by Kumar et al. [35] described that bupivacaine addition to opioids proved beneficial in a selected patient population with pain refractory to IT opioids alone. In their patient population (n = 19) with mixed nociceptive and neuropathic pain, addition of bupivacaine restored pain control and improved activity level and quality of life. Deer et al. examined the effect of bupivacaine in a retrospective study of 109 patients (25 with cancer pain, 84 with noncancer pain) who received IT O infusions [32]. All patients had received IT Os alone (morphine, average dosage of 8 mg/day, or hydromorphone; average dosage 1.5 mg/day) before being switched to an opioid-bupivacaine (average 10 mg/day, range 2–25 mg) combination. Bupivacaine was added to the infusate of those treated with the opioid alone because of inadequate analgesia. Patients who had a poor response to the opioids alone and were then switched to opioid-bupivacaine combinations reported significantly lower pain scores and experienced a mean opioid dosage reduction of 23%. No major adverse effects and no changes in neurologic exams were reported in patients exposed to opioid/bupivacaine combinations.

In a randomized, double-blind, multiple-phase crossover trial of 24 patients with chronic noncancer pain, the addition of bupivacaine to morphine or hydromorphone produced a statistically significant improvement in quality-of-life scores [34]. However, neither a dose-response nor a significant effect on pain scores was observed. For 4 months, patients received IT infusion of four different drug combinations (opioid alone or consecutively with...
three different bupivacaine concentrations. Every month, pumps were refilled with either the same opioid they received prestudy, or its mixture with bupivacaine. In random order, patients thus received placebo or bupivacaine (4, 6, or 8 mg/day) plus morphine sulfate (4–22 mg/day) or hydromorphone (7–22 mg/day). Only bupivacaine 6 mg/day produced improvements in quality-of-life scores. One patient reported mild adverse effects from IT bupivacaine (mild numbness in the lower extremities without weakness). Unlike our study, bupivacaine was added to the pumps of patients already receiving long-term IT O therapy. Our results suggest that placing patients on dual medication (opioid and local anesthetic) from the outset of IT therapy may be advantageous in blunting opioid dose escalation.

In a prospective cohort study, van Dongen et al. reported [37] that five of 20 cancer patients who had inadequate analgesia with ITm alone reported improved pain relief when bupivacaine 5–21.6 mg/day was added to the infusate. ITm dosages ranged from 1.2–7.2 mg/day, with a mean treatment duration of 85 and 58 days for the groups receiving morphine alone and morphine/bupivacaine, respectively. The combination of morphine and bupivacaine resulted in a diminished progression of the ITm dose escalation during the phase of stable analgesia in comparison with the morphine only group. The investigators reported subjective weakness in the legs and arms of two of the five patients who received a morphine/bupivacaine combination. However, no serious adverse effects were reported and patients were followed until death.

The significance of the current study rests on the fact that blunting opioid dose escalation results eventually in lower opioid doses and concentrations necessary to maintain pain relief. Higher opioid doses/concentrations may result in IT granuloma formation and potentially in opioid-induced hyperalgesia.

Expert panels have presented algorithms for drug selections based on available clinical evidence [1]. Recently, consensus guidelines were developed regarding the evidence required to support the use of a specific drug or a combination therapy for long-term infusion [4]. Combination of ITm or hydromorphone with bupivacaine was ranked as a second-line therapy. Our study suggests that initial combination therapy (rather than adding bupivacaine after the primary opioid has failed) is beneficial in blunting opioid dose escalation. Opioid/bupivacaine combination IT therapy should be considered early on especially in younger noncancer pain patients with fairly localized pain, such as persistent low back pain after previous lumbar spine surgery, as it may blunt opioid dose escalation and its untoward consequences.

Prospective trials are necessary to thoroughly examine the phenomenon of IT opioid dose escalation and the effects of addition of bupivacaine to IT opioids particularly in FBSS. Such studies would establish safety and efficacy of bupivacaine as an adjunct medication to IT opioids, and define its effects and clinical utility in the various settings in which IT therapy is considered. That would be a tall task to achieve given that bupivacaine is not currently FDA approved for IT use and given the currently available single-chamber IT pumps.

References


