Implantable Intrathecal Pumps for the Treatment of Noncancer Chronic Pain in Elderly Population: Drug Dose and Clinical Efficacy

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ABSTRACT

Objective. This study aims to assess long-term follow-up of efficacy and quality of life for 34 geriatric patients (10 men, 24 women, mean age 72.3 ± 11.6 years) with intrathecal (IT) drug delivery systems (IDDS), implanted between 1994 and 2002, for the treatment of severe noncancer chronic pain. Methods. Patients equal to or older than 64 years, who had no pain relief after administration of a placebo injection (subcutaneous saline), and who responded positively to an IT trial (morphine and bupivacaine at low doses) with pain relief greater 70% without intolerable adverse effects were included into our study. Clinical assessment forms and questionnaires assessing pain intensity, adverse events, complications, concommitent use of analgesics, and doses of IT drugs administered were filled out by our patients prior to and after IT drug delivery implantation. Results. Pain intensity was substantially reduced (60%) at three-month follow-up after commencing IT therapy and was consistently reduced at 48-month follow-up. The mean visual analog scale (VAS) value decreased from 8.09 (± 1.25) before implantation to 1.68 (± 0.63) after implantation at 48-month follow-up. This benefit, at 48 months, was achieved using mean low doses of IT morphine and bupivacaine, 1.03 ± 0.61 mg and 1.15 ± 0.58 mg, respectively. Only two out of 34 patients (5.9%) had complications related to the implantation procedure, itself. Side-effects of therapy were reported by 50% of the patients, the most frequent being constipation (34.4%), drowsiness (21.9%), nausea (21.9%), and urinary retention (18.8%). No side-effects of therapy resulted in removal of the IDDS. Conclusion. The use of IT drug delivery through IDDS for the treatment of non-cancer- and cancer-related pain in geriatric patients is successful.

KEY WORDS: IT therapy, noncancer chronic pain, pain management.

Introduction

Recently, there has been an increasing interest in the use of IT therapy for pain therapy for patients who do not receive adequate pain control with traditional methods of drug administration or for those who do not tolerate high doses of orally administered opioids because of systemic side-effects. Reports have been published describing the treatment of cancer and noncancer pain with this technique (1).
There are several clinical advantages to intrathecal (IT) therapy for pain control. Because there is a slow replacement of the cerebrospinal fluid (CSF) over time, morphine, when delivered IT and its metabolites, especially morphine-6-glucuronide, provide prolonged analgesic (2–4). The use of IT bupivacaine for the treatment of noncancer chronic pain has also been widely described and studied and has been shown to be free of bone marrow toxicity and to have positive synergy with opioids (5,6). Because local anesthetics and opioids work on differing analgesic systems, low doses of these agents, when added to each other IT, provide analgesic synergy (7). Moreover, the use of a low dose of bupivacaine when added to IT morphine allows for a low dose of morphine, thereby reducing the incidence of opioid-related side-effects (8).

Although morphine is the gold standard agent used for IT therapy, experts in the field of IT therapy today use a variety of drug combinations, such as morphine/bupivacaine, hydromorphone, and morphine/clonidine (7,9), but a clear standard for the correlation of a specific combination of drugs to the treatment of a specific type of pain is still lacking. An effective dose of opioids is variable and individual to the needs of each and every patient; however, the effective dose of any one opioid often reaches high levels for various reasons including syndrome-specific opioid resistance, receptor phenotype-determined resistance, and/or tolerance to the opioid delivered. Appropriate patients are selected for IDDS using IT/epidural trials either by single shot injection or titration through an implanted catheter until effective dosage is reached (9).

The IT administration of low-dose agents for the attainment of satisfactory pain control is particularly important for the geriatric population. Nowadays, the number of elderly people and the average age of the population are increasing. The elderly often suffer from age-related diseases such as vascular cardiopathies, cerebrovascular diseases, osteoporosis, and arthritis, which are, in themselves, allergenic (10) and from pneumonias, diabetes, peripheral arterial diseases, and fractures, which generate further pain (11). These diseases result in serious disabilities and limitation of patients’ physical, cognitive, and social activities, resulting in loss of the autonomy and worsening of their quality of life. For this reason, it is of primary importance to find an efficient analgesic therapy for the elderly that avoids pharmacologic interactions with other medications used by patients for the treatment of their comorbid diseases that result in unwanted effects and adverse events.

It is also well-established that the elderly (older than 64 years) need lower doses of drugs to achieve the same level of efficacy that younger patients need. The aging process, indeed, involves a series of metabolic modifications that result in important alterations of the pharmacokinetics and dynamics of a drug (12). In particular, the reduction of body water level results in a reduced distribution of hydrophilic drugs, such as morphine. Similarly, the age-related reduction of plasma proteins causes an increase in the concentration of active drug and, hence, a reduction in drug dosage needed. Moreover, the decrease of renal and hepatic output requires an adjustment of drug dosages given to the elderly (13,14).

It was the aim of our study to evaluate and assess the use of IT opioids combined with IT local anesthetics for pain treatment in a geriatric population. It was the secondary aim of this study to evaluate the mean lowest IT dose possible in this study group, an important fact to ascertain because, as a group, the elderly have more side-effects to pharmacologic management than a similar group of patients who are of median age.

Materials and Methods

Subjects
We performed a retrospective analysis of efficacy and safety data on 34 geriatric patients (ages 65–86 years) suffering from chronic non-cancer-related pain, who underwent implantation with IDDS systems for IT therapy between the years, 1994–2002. All implantations were carried out under local anesthesia. The IDDS systems used included Archimedes (Anschütz, Kiel, Germany) in two patients, Tricumed (Anschütz) in six patients; Isomed (Medtronic Inc., Minneapolis, MN, USA) in 24 patients and Synchromed (Medtronic Inc.) in two patients. In this group, there were 12 patients with peripheral neuropathic pain (diabetic neuropathy or complex regional pain syndrome type I), 11 with nociceptive pain (osteoartegenerative spinal stenosis and low back pain) and nine with neuropathic-nociceptive pain (failed back surgery syndrome). All patients reported a visual analog scale (VAS) intensity of greater than six for at least one year and had failed more conservative therapies to control basal pain levels and phases of acute pain. Patients with nociceptive pain (11) and nociceptive-neuropathic pain (9) had received prior infiltrative therapies such as intra-articular infiltrations and peridural blocks with corticosteroids and anesthetics and oral opioids without any benefit or the development of severe, intractable side-effects. Seventy percent of the patients with nociceptive pain and 30% of the patients with neuropathic pain did derive benefit from their oral opioids; however, the development of side-effects such as over sedation resulted in discontinuance of the therapy (12). The group with neuropathic pain (12) also trials for spinal cord stimulation without benefit (5), or had developed tolerance (7) to the effect of spinal cord stimulation (after around six years). Transcutaneous electrical nerve stimulation was used in four patients suffering from low back pain. All patients in our study group
responded positively to an IT morphine infusion trial, reporting a reduction of greater than 70% from the initial VAS for pain value. The following patients were excluded from our study:

- Patients younger than 65 years old;
- Patients with a personality disorder;
- Patients who underwent implantation with IDDS for spasticity;
- Patients suffering from cancer pain or central neuropathic pain (central neuropathic pain is known not to be responsive to opioids and local anesthetics);
- Patients unresponsive to a trial of efficacy for IT therapy with opioids/bupivacaine;
- Patients who developed intolerable adverse effects (especially those affecting respiration and diuresis) during the trial for IT efficacy;
- Patients allergic to opioids or local anesthetics;
- Patients suffering from chronic abuse of drugs that act on the central nervous system; and
- Patients who required clonidine or other adjuvant other than bupivacaine for control of pain. Clonidine was administered in association with morphine to patients who developed tolerance to morphine or who had pruritus as an adverse event to the delivery of IT morphine. Bupivicaine, however, was administered as an adjuvant to morphine when VAS scores were not controlled during the IT trials with morphine alone, in particular, when the VAS was reduced less than 50%.

We limited this retrospective analysis to patients receiving morphine and bupivacaine because the addition of patients with other combinations of agents would have complicated our analysis, rendering interpretation of results almost impossible. Our study was limited to answering the questions of whether IT morphine or IT bupivacaine/ morphine was efficacious in this population of elderly patients at doses that were both efficacious and low.

**Trial Technique**

Before implantation of a permanent IDDS system, a trial was performed to assess efficacy and tolerability of intraspinal analgesia infusion. We, as is our usual and customary procedure, performed the trial with single intrathecal injections of drug at L2–3 via a 27-gauge Whitacre spinal needle (Becton Dickinson Caribe Ltd., Juncos, Puerto Rico) in the sitting position. The clinician performing the trial also evaluated whether the placebo injection or the injection of the active agent resulted in pain relief, according to the customary procedures of our department, but was not involved in data recording and/or treatment for opioid-related side-effects. All patients and doctors, who recorded the data and treated therapy-related side-effects, were blinded to whether a placebo or active agent was administered. Agents used for this trial included either morphine 0.1 mg and isobaric bupivacaine (0.5%) 0.125 mg, given IT, or a paraspinous subcutaneous administration of saline solution (2 mL).

This trial for efficacy and safety lasted seven days. Placebo or morphine/bupivacaine IT injections were administered to patients on days 1, 3, and 7 of the trial. Patients were considered to be positive responders to IT analgesia if they received pain relief greater than 70% after administration of morphine and bupivacaine, and less than 30% after injection of the placebo. The dose of morphine/bupivacaine that provided relief of pain during the trial was the initial dose used at implantation.

At each subsequent visit to our pain unit, we evaluated the patient’s residual pain complaint and modified the dose of morphine/bupivacaine using the following protocol:

- If the pain was not adequately controlled at a dose of 0.5 mg/day of morphine (evaluated as a VAS 0–10 reduction of less than three points), 0.5 mg/day of bupivacaine was added to morphine infusion.
- The bupivacaine dose was increased by 0.25 mg/day until a reduction of at least three points in VAS was observed. After two increases of bupivacaine dosage, if the VAS reduction was still less than three points, then the dosage of morphine was increased (maximum dosage 1.0 mg/day, as above described).

Patients were generally evaluated monthly, when they came to the clinic to refill the pump. Extra visits were made every time the patient did not achieve a satisfying pain control, in this case a change in the drug dosage was allowed. The data shown in this paper were collected only at selected time points (as described in the next paragraph) from the clinical files of patients.

**Data Collection**

Using questionnaires, the following variables were evaluated by our clinicians at each visit: pain intensity (VAS, 0–10), dose of IT drug (morphine or bupivacaine), incidence of side-effects, and complications. Each variable was evaluated at different time points: before implantation ($t_0$) and at 3, 6, 12, 18, 24, 36, and 48 months after implantation ($t_1$–$t_7$). At each time point, the mean and the standard deviation of VAS and dosage of drugs used were computed.

**Data Analysis**

For VAS values and drug doses used, the means and standard deviations were computed. A paired $t$-test was used to analyze the significance of changes observed in VAS values and morphine and bupivacaine doses at each time point in respect to the previous time point ($p < 0.05$ was considered significant).
TABLE 1. Characteristics of the Sample

<table>
<thead>
<tr>
<th></th>
<th>Sample (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.3 ± 11.6</td>
</tr>
<tr>
<td>Gender</td>
<td>65–86</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>10 (31.3%)</td>
</tr>
<tr>
<td>Females</td>
<td>22 (68.7%)</td>
</tr>
<tr>
<td>Type of pain</td>
<td></td>
</tr>
<tr>
<td>Neuropathic</td>
<td>12 (37.5%)</td>
</tr>
<tr>
<td>Nociceptive</td>
<td>11 (34.4%)</td>
</tr>
<tr>
<td>Neuropathic-nociceptive</td>
<td>9 (28.1%)</td>
</tr>
</tbody>
</table>

Results

Our initial study sample was 34 patients; however, because of infections, two patients (5.8% of the sample) dropped out of the study. Our final sample for analysis was 32 patients (10 men and 22 women) (Table 1). Our results for mean values and standard deviations of VAS pain and morphine and bupivacaine doses are reported in Table 2 and Figs 1–3.

Pain Relief

The initial VAS intensity of pain for each patient was assessed before implantation at time 0 (t₀). The mean VAS value at t₀ was 8.01 ± 1.25 and after three months of IT therapy, at time 1 (t₁), the mean value for VAS had decreased to 3.21 ± 2.04, a reduction in pain intensity of 60%. There were no significant changes in the VAS until 18 months after initiating therapy at t₀ when it reached a mean value of 2.47 ± 1.54. Further decreases in the VAS were observed after 36 months (t₆). VAS t₆ = 1.96 ± 1.25 and 48 months (t₇). VAS, t₇ = 1.28 ± 0.63, representing a reduction in pain intensity of 85% from t₀ (Table 2 and Fig. 1).

Morphine Dosage

The average morphine dose administered to patients before implantation at t₀ was 0.41 ± 0.28 mg/day. After a slight increase at three months (t₁) of IT therapy (0.51 ± 0.33 mg/day), the mean morphine dose remained constant for up to 36 months (t₆) when the mean dose had reached 0.89 ± 0.57 mg/day. At t₇, at 48 months of therapy, the dose had increased to 1.03 ± 0.61 mg/day. These figures at t₆ and t₇ correlated well with the decrease seen in the VAS as described in Table 2 and Fig. 2. The number of patients receiving morphine alone decreased progressively over time from 23 at t₀ to 11 at t₇ (Table 3). Twelve patients had shifted from morphine alone to morphine bupivcaine t₀ to t₇.

TABLE 2. Visual Analog Scale (VAS) Score and the Dose of IT Drugs (Morphine and Bupivacaine) From t₀ to t₇ (Respectively Before the Implantation and at 3, 6, 12, 18, 24, 36, and 48 Months After Implantation)

<table>
<thead>
<tr>
<th></th>
<th>t₀</th>
<th>t₁</th>
<th>t₂</th>
<th>t₃</th>
<th>t₄</th>
<th>t₅</th>
<th>t₆</th>
<th>t₇</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS mean ± SD</td>
<td>8.01 ± 1.25</td>
<td>3.21 ± 2.04</td>
<td>3.12 ± 1.33</td>
<td>3.43 ± 1.75</td>
<td>2.46 ± 1.54</td>
<td>2.37 ± 1.38</td>
<td>1.96 ± 1.25</td>
<td>1.28 ± 0.63</td>
</tr>
<tr>
<td>Morphine dosage mean (mg/day) ± SD</td>
<td>0.41 ± 0.28</td>
<td>0.51 ± 0.33</td>
<td>0.69 ± 0.40</td>
<td>0.76 ± 0.39</td>
<td>0.81 ± 0.50</td>
<td>0.82 ± 0.54</td>
<td>0.89 ± 0.57</td>
<td>1.03 ± 0.61</td>
</tr>
<tr>
<td>Bupivacaine dosage mean (mg/day) ± SD</td>
<td>0.66 ± 0.12</td>
<td>0.6 ± 0.17</td>
<td>0.9 ± 0.67</td>
<td>0.82 ± 0.48</td>
<td>1.03 ± 0.70</td>
<td>1.05 ± 0.49</td>
<td>1.15 ± 0.61</td>
<td>1.15 ± 0.58</td>
</tr>
</tbody>
</table>
Bupivacaine Dosing

The number of patients requiring the addition of bupivacaine to morphine varied during the different follow-up periods (Table 5). At $t_0$, nine patients required the addition of bupivacaine. At $t_2$, 19 patients required an addition of bupivacaine to improve analgesia and at $t_7$, 35 months after implantation, 21 patients required an addition of bupivacaine to improve analgesia and at $t_7$, 35% of the total sample (32 patients) received only morphine, whereas 65% of them required the addition of bupivacaine to morphine.

The average dose of bupivacaine did not vary significantly during follow-up periods, starting at $0.66 \pm 0.12 \text{ mg/day at } t_0$ and reaching a maximum mean value of $1.15 \pm 0.58 \text{ mg/day at } 48 \text{ months (t}_7\text{)}$ after implantation (Fig. 3).

Complications and Side-Effects

Complications were observed in two patients out of the 34 enrolled. One patient had septic meningitis as a consequence of refilling his IDDS. This patient required urgent removal of the entire implanted system and was excluded from our study and data collection. Another patient had a constant slight increase in body temperature without central effects for 12 months after implantation that correlated with the presence of fluid in the pocket around the pump and for this reason the IT catheter and IDDS removed. This patient also was excluded from the study.

Side-effects of the drugs infused were experienced by 16 out of 32 patients (50%) (Table 4). Only one side-effect was reported in 9.5% of patients, while the remaining patients had two or more side-effects (Table 5). The most frequent side-effect of IT therapy was constipation (34.4%), followed by nausea (21.9%) and drowsiness (21.9%), urinary retention (18.8%), itching (15.6%), vomiting (12.5%), dizziness (12.5%), loss of appetite (12.5%), diarrhea (3.1%), xerostomia (3.1%), and impotence (3.1%). There were no side-effects that could be directly correlated to the use of bupivacaine, such as hypotension and/or cardiotoxicity.

Discussion

Recently, several studies regarding the use of IT infusion therapy have been published (15–18). This suggests that long-term IT infusions of opioids are increasingly used as

### TABLE 3. Number of Patients Receiving Morphine and Bupivacaine or Morphine Alone for the Infusion IT Therapy at Each Time Point (From $t_0$ to $t_7$: Before the Implantation and at $3, 6, 12, 18, 24, 36$, and $48$ Months After Implantation, Respectively)

<table>
<thead>
<tr>
<th>Time</th>
<th>Morphine + Bupivacaine ($N = 32$)</th>
<th>Morphine ($N = 32$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_0$</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>$t_1$</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>$t_2$</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>$t_3$</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>$t_4$</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>$t_5$</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>$t_6$</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>$t_7$</td>
<td>21</td>
<td>11</td>
</tr>
</tbody>
</table>
The efficacy of IT administration of opioids for untreatable pain is well documented in the literature (7,14–17,21,22). Guidelines for dosing adjustments, IT drug trials, and management of drug-related side-effects and symptoms have also reported (7,23). Several authors report the use high dosages of drugs for IT therapy for the treatment of pain in nongeriatric patients (14,16,17,24–26). For example, Roberts and colleagues studied 80 patients with noncancer pain in nongeriatric patients (14,16,17,24–26). For example, Roberts and colleagues studied 80 patients with noncancer chronic pain and reported that their average morphine dose was 9.95 ± 2.52 mg/day after six and 36 months of IT therapy, respectively (17). Tutak and Doleys assessed 26 patients (average age 44.3 years) with noncancer chronic pain and reported that their average morphine dose was 1.38 and 9.54 mg/day after three and 21 months of IT therapy, respectively (20).

The most common side-effects reported were constipation (34.4% of all patients) followed by nausea and drowsiness (21.9%) and then urine retention (18.8%). Less reported side-effects included pruritis (15.6%), vomiting (12.5%), dizziness (12.5%), loss of appetite (12.5%), diarrhea (3.1%), xerostomia (3.1%), bradypnea and respiratory depression (3.1%), and impotence (3.1%) (Table 4). Interestingly to us, no patients reported direct side-effects, a relatively high incidence, even at low doses. The most common side-effects reported were constipation (34.4% of all patients) followed by nausea and drowsiness (21.9%) and then urine retention (18.8%).

The reported incidence of complications following IT therapy is significant; various technical complications such as movement or malfunctioning of the catheter and lead twisting, leading to suspension of therapy in 3.1% of cases, have been reported after implant (range: 37–2.7%) and long-term follow-up studies (range: 8.7–7.2%) (25). Other authors, such as Anderson and Burchiel, have reported an device related complication incidence of 20% (18,22,24,26).

Our study showed that IT therapy in this population of patients is safe. Indeed, only two patients of 34 enrolled (5.88%) had serious complications requiring cessation of therapy. Moreover, and more significant, 16 out of 32 patients that finished the study (50%) experienced no side-effects. The 16 patients who did experience side-effects usually had more than one side-effect at any one time and none was serious; only 3 out of 16 (9.5%) reported only one side-effect (Table 5).

The purpose of our study was to investigate whether a geriatric population of patients require lower doses of IT analgesic drugs when compared to those doses required by less elderly populations (14). In our study, a VAS reduction of 60% was achieved in a geriatric population at three months of therapy and maintained over time. There was a reduction of the mean VAS from 8.01 ± 1.25 to 3.21 ± 0.63 after three months and to 1.28 ± 0.63 after 48 months of IT therapy (85% reduction). The morphine dose required to provide adequate analgesia in this population of patients did not change significantly for up to 36 months, suggesting that the analgesic effect of morphine remained constant. The increase in morphine dose needed and observed at 36 and 48 months (0.89 ± 0.57 and 1.03 ± 0.61 mg/day, respectively), resulted in a significant decrease in the VAS (Table 2 and Fig. 2) that could be correlated to the onset of a low level of tolerance.

Morphine alone sufficed for 35% our patients for the entire study period, whereas 65% of our study patients needed the addition of bupivicaine at different stages of the study to provide adequate analgesia. In order to provide improved pain control while keeping the doses of morphine stable, bupivicaine was added to morphine for patients who reported a VAS = 4 at follow-up visits. At the same time, bupivicaine dosages were maintained at low levels (max. 1.15 ± 0.58).

Our study, when compared to the studies in younger patients of Roberts (17) and Tutak and Doleys (20), showed that elderly patients need lower doses of IT morphine when compared to younger populations for pain control. Moreover, Franco Gay (22) studied 39 patients with nonmalignant pain. Of these 39 patients, 13 were assessed for more than 36 months (mean age 63.4 ± 11.4 years, range: 39–77) and all had significant pain reduction following IT therapy with an average morphine dose of 1.9 ± 1.9 mg/day (range: 0.4–7.2 mg/day). Geriatric patients (72.3 ± 11.6 years) enrolled in our study attained similar benefits with low-dose morphine, 0.89 ± 0.57 and 1.03 ± 0.61 mg/day after 36 (t6) and 48 (t7) months of therapy, respectively. These results suggest that elderly patients have high sensitivity to IT opioid administration. It is our contention that the dose of IT drugs for pain control in elderly populations should be low at the initiation of therapy, and if an adjustment is needed, that adjustment should be made slowly to avoid undesired side-effects.

Conclusions

In conclusion, patients in our study achieved significant pain relief at low doses of morphine and bupivicaine when delivered IT in a population of elderly patients with
noncancer-related pain. Our patients had significant reductions in their VAS (60%) at three months of therapy, a reduction, which remained constant for a considerable amount of time. Technical complications were very few; however, side-effects that were not therapy limiting were present in 50% of our patients.

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We acknowledge the Institute of Algological Science for present in 50% of our patients.

**References**