Dual Device Therapy (Spinal Stimulation and Intrathecal Drug Delivery) for Treatment of Multi-Focal Pain

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INTRODUCTION

Implantable drug pumps for the treatment of pain were first reported by Onofrio et. al. in 1981 and have become a common treatment for patients with intractable chronic non-malignant pain refractory to oral medications as well as for cancer pain.[1] For many years, pumps were used to only treat nociceptive pain, however recently pumps are also being used in patients with neuropathic pain. Spinal stimulation is an accepted treatment for neuropathic pain in the trunk and extremities. A subset of patients require treatment with both spinal cord stimulation and intrathecal infusion. Dual modality therapy has become increasingly more common as physicians gain experience with each modality used separately. An FDA-approved clinical study of a novel drug pump (Prometra®, InSet Technologies, Mt. Olive, NJ, USA) allows the prospective evaluation of this dual-therapy population. The subset of patients with both spinal stimulators and intrathecal pumps may have better control of both their neuropathic and nociceptive pain than those with only one system. Clinical data from the PUMP Study are presented. Dual-therapy patients will be compared to patients with only spinal pumps to determine if there are measurable differences in pain measures and complications.

METHODS

Protocol

The PUMP Study is a prospective, open-label study evaluating the accuracy, efficacy and safety of the Prometra Pump System in treating pain using morphine sulfate. The study is fully enrolled. One-hundred-ten patients were enrolled in the PUMP Study at seven clinical sites. Of those 21 (19%) have a concurrent stimulator at six clinical sites as described in Table 1. As of November 1, 2008, this population represents 9,435 device-days (26 years) of clinical experience. Baseline data are collected pre-implant and follow-up is monthly for the first six-months post-implantation and every three months thereafter. Data collected includes adverse events, pain and disability scores (VAS, NRS, ODI), as well as longitudinal intraspinal and systemic morphine dosing. Accuracy of drug delivery was also collected; accuracy was calculated by dividing the total measured delivered volume by the total volume programmed for delivery. Data are being tabulated by an independent third party (inVentiv Clinical Solutions, The Woodlands, TX).

Table 1: Enrollment of Patients with Concurrent Stimulator

Clinical Site	Location	Primary Investigator	Number of Subjects
Center for Interventional Pain Management	St. Louis, MO	Gurpreet Padda	7
Fox Chase Pain Management Associates	Jenkintown, PA	Steven Rosen	5
Wake Forest University Health Sciences	Winston-Salem, NC	Richard Rauck	4
Pain Institute of Tampa	Tampa, FL	John Barsa	2
The Center for Pain Relief	Charleston, WV	Timothy Deer	2
Pain Control Network	Louisville, KY	Elmer Dunbar	1
		Total 21	

Patient Population

Table 2: Demographics and Pain History

	Total (N=21)
Age (years) at implant	50.6 ± 10.8 (34-72)*
Gender	11 males, 10 females
Duration of Pain (years)	13.8 ± 8.9 (2-35)*
Pain Category**	
NEUROPATHIC	11
NEUROPATHIC AND NOCICEPTIVE	9
NOCICEPTIVE	1
Pain Cause**	
POST LUMBAR SPINE SURGERY WITH PAIN	12
COMPLEX REGIONAL PAIN SYNDROME	11
INTRACTABLE BACK PAIN	9
ARACHNOIDITIS	5
POST CERVICAL SPINE SURGERY WITH PAIN	4
VERTEBRAL BODY COMPRESSION FRACTURES	1
OTHER	12
Areas of Involvement	
GENERALIZED	4
LOCALIZED**	17
BACK	11
LEGS/FEET	11
ARMS/HANDS	7
HIPS	7
SHOULDERS	7
NECK	6
HEAD	4
CHEST	2
OTHER	3

*Data presented as mean ± standard deviation (range)
**Items in these categories are not mutually exclusive

Pumps were programmed to an average daily dose of 6.13 mg ± 4.01 (mean ± standard deviation). The range in programmed daily dose was 0.25 mg to 13.86 mg.

METHODS

Device Description

The Prometra Programmable Implantable Pump is being developed by InSet Technologies Incorporated of Mt. Olive, NJ.

The Prometra is a pressure driven pump. This type of design should provide a number of improvements over older generation pumps, as follows:

- Very accurate drug delivery
- Micro volume delivery capability
- Long device life due to few moving parts and an energy-efficient design
- Relative light weight
- Ability to deliver advanced compounds, such as large proteins

The Prometra contains a metal bellows drug reservoir with a capacity of 20 mL. The reservoir propellant is stored within the rigid housing surrounding the bellows and provides the driving pressure for the pump. The driving pressure on the reservoir forces drug through an outlet filter, and into an electronically controlled flow metering valve-accumulator subsystem. The drug passes from the flow metering subsystem, into the catheter access port then into the catheter for delivery to the intrathecal space. The teardrop shape of the pump is designed to help the clinician differentiate the catheter access port from the central access port after the pump is implanted. The drug chamber is refillable and is percutaneously accessed via the centrally located access port using a 22-gauge non-coring needle. The catheter access port is located on the periphery of the pump to allow for direct access to the catheter without interfering with the drug reservoir. The catheter access port can be used to evaluate catheter patency or catheter placement.

RESULTS

Accuracy

Patients in this population had a total of 197 refill visits and, depending upon implant date, had between 1 to 18 visits per patient. The mean accuracy in drug delivery was determined to be 98.6% (90% confidence interval: 97.2% to 100.0%).

Complications

There have been no deaths in this population.

Adverse events reported to be device or procedure-related include procedural pain (8), pain (4), implant site pain (3), wound secretion (3), dizziness (2), implant site edema (2), implant site erythema (2), implant site swelling (2), balance disorder (1), headache (1), implant site bruising (1), nausea (1), peripheral edema (1), post lumbar puncture syndrome (1), pruritus (1), pump pocket tenderness (1), rash (1), respiratory depression (1), scabs on incision (1), seroma (1), surgery to replace catheter (1), and vomiting (1). All events have resolved; none were reported to be serious.

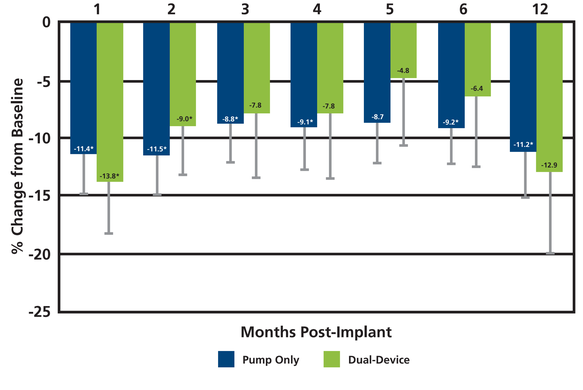
Device complications include catheter migration (3), pump refill error (3), delayed priming (2), programmer difficulty (2), catheter coiled upon insertion (1), pump access difficulty (1), pump migration (1), pump-programmer communication error (1), and serial number not in pump memory (1). The complication for catheter migration remains under observation (the catheter remains in the intrathecal space and the patient's pain improved after an increase in morphine dose); all other complications have been resolved.

Two patients elected to have their Prometra Systems explanted due to a perceived lack of efficacy.

Patient Outcomes

Oswestry Disability Index (ODI) Scores improved over time as shown in the following graph. Improvements were significant in the first two months for the dual-device patients; improvements were significant at all visits except Month 5 for the pump-only patients.

Figure 1: Mean ODI Score by Visit: Pump Only and Dual-Device Patients

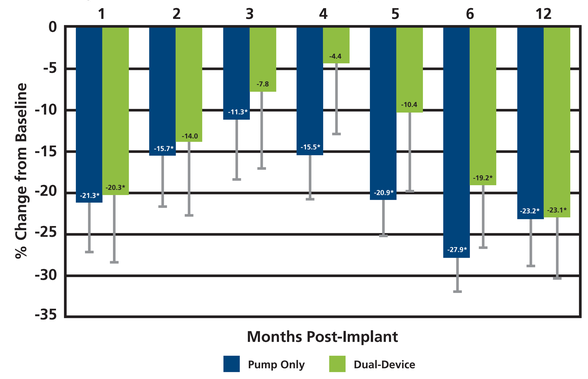


*Significant (p<0.05) using Wilcoxon Signed-Rank test.
Data shown is mean ± standard error of the mean.
ODI is based on a value of 0-100. It assess level of disability in activities of daily living in patients with chronic pain.
A negative percent change indicates an improvement.

RESULTS

VAS pain scores improved over time as shown in the following graph. Improvements were significant at Month 1, Month 6, and Month 12 for the dual-device patients; improvements were significant at all visits for the pump-only patients.

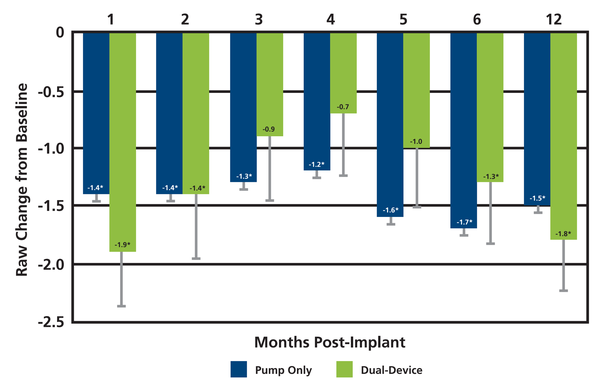
Figure 2: Mean VAS Score by Visit: Pump Only and Dual-Device Patients



Data shown is mean ± standard error of the mean.
VAS score is based on a scale of 0-100 where 0 indicates no pain and 100 indicates worst pain imaginable.
A negative percentage change indicates improvement (reduction in pain).

Pain levels as reported by the NRS improved over time as shown in the following graph. Improvements were significant at Month 1, Month 2, Month 6, and Month 12 for the dual-device patients; improvements were significant at all visits for the pump-only patients.

Figure 3: Mean NRS Score by Visit: Pump Only and Dual-Device Patients

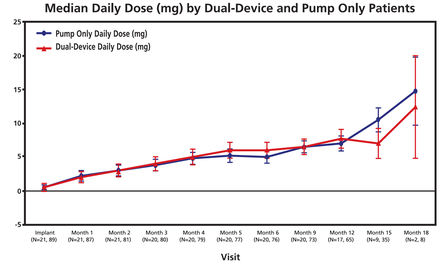


*Statistically significant (p<0.05) using Wilcoxon Signed-Rank test.
Data shown is mean ± standard error of the mean
NRS score is based on a scale of 0-10 where 0 indicates no pain and 10 indicates worst pain imaginable.
A negative percentage change indicates improvement (reduction in pain).

Morphine Dosage/Flow Rates:

Daily programmed morphine dosage and morphine concentration was compared between the dual-device population and the pump only population. Increases from implant were noted in median daily dose in both populations at each visit.

Median Daily Dose (mg) by Dual-Device and Pump Only Patients



The raw change in median daily dose was tested for differences from zero using the Wilcoxon Signed-Rank test. All changes were statistically significant.

RESULTS

Comparison of Populations

An analysis was performed to ascertain if there were any differences between the dual-device population and the pump-only population. Fisher's exact test was used for categorical parameters and Willcoxin Rank test for continuous variables. The following variables were included in the analysis: gender, catheter tip location, type of pain, pain category (neuropathic or nociceptive), age, daily morphine dose, morphine concentration, % change on VAS, raw change on NRS, duration of implant, adverse events or device complications. Significant differences were seen in the type of baseline pain reported. Pump-only patients had higher reports of aching pain (p=0.0372), while dual-device patients had higher reports of burning pain (p=0.0276). No differences were seen in other types of pain (pins and needles, sharpness, numbness, and cramping) that were reported. Statistically significant differences were also seen in the adverse events reported; a smaller percentage (91%) of patients in the dual-device group reported adverse events, as compared to the pump-only patients (100%) (p=0.0350). No differences were detected in device complications reported between the two groups. No significant differences were seen in any of the other categories listed above.

DISCUSSION

Both dual-device and pump-only patients noted improvement in pain scores at one month. The pain benefit decreased by the fourth month and then increased at one year. These changes may be partially explained by one patient who had poor pain relief throughout the study. This patient chose to have their Prometra System explanted prior to the Month 12 visit due to perceived lack of efficacy. Previous studies have shown a trend towards increasing dose needed to maintain pain relief.[2,3] Pump dosing increased during the study but pain relief was maintained in both dual-device and pump-only patients. Complication rates were low and similar to previous studies.[4] Catheter dislodgement occurred in three patients, but the rate decreased as the study continued, indicating that this was probably secondary to the investigators' learning curve. No intrathecal granulomas were identified.[5]

The Prometra pump was 98.6% accurate. This improved accuracy may turn out to be clinically significant in patients with spinal polypharmacolgy, especially where the therapeutic windows may be small (e.g., ziconotide, baclofen).[6]

No significant difference in outcomes or complications has been noted in patients with pump-only or dual-device therapy. No previous studies have specifically followed patients with both implantable devices. It has been suggested that catheter-tip fibromas may be more prevalent in patients with dual-device therapy, however this complication has not yet been observed.

CONCLUSION

Dual-therapy with both implantable spinal pumps and stimulators is a viable option in patients with both nociceptive and neuropathic pain. There was an improvement in pain/disability measures (VAS, NRS, ODI) by one month. Similar levels of improvement were still observed at one year. Morphine dosing increased during the study, consistent with results noted in previous studies. Pump accuracy was 98.6%. No unexpected complications were noted. Dual-device patients appear to behave similarly to pump-only patients in terms of both pain relief and complications.

The Prometra pump is a viable option in patients who have pre-existing spinal stimulators and mixed neuropathic and nociceptive pain. Pain control occurs at one month and is maintained at twelve months in this group of patients.

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