Efficacy Of Morphine Sulfate Infusion Via The Prometra® Programmable Intrathecal Pump: A Prospective Multi-Center Evaluation

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INTRODUCTION

Decreased pain levels and disability are the primary desired outcomes when treating patients with an implantable infusion pump and accuracy of the drug delivered by the pump is a very important therapeutic component. Pumps that are currently market-approved are labeled for accuracy of ±14.5%. The Prometra pump has a number of design elements that should improve accuracy, including:

- Non-compliant dosing chamber that provides meticulous measurement (no rollers)
- Precise, controlled drug flow with electronic dual gated system
- A reservoir that acts as a volume-control regulator in micro increments
- An isolated valve system robust to temperature and pressure changes
- Ability to completely shut down (zero flow)

During a prospective, multi-center, FDA-approved clinical study (Prometra's Utilization in Mitigating Pain, or PUMP), the accuracy of drug delivery and the efficacy of treatment were evaluated.

METHODS

Device Description

The Prometra Programmable Pump, developed by InSet Technologies Incorporated (Mt. Olive, NJ) is a pressure-driven, calibrated, microdosing pump. This type of design is expected to provide a number of improvements over older generations of programmable pumps. In addition to improved accuracy, it is expected to have microvolume delivery capability, a long device life (due to few moving parts and energy-efficient design), relative light weight, and the ability to deliver advanced compounds, such as large proteins.

Protocol

The PUMP study was a prospective, open-label evaluation of the Prometra Programmable Pump System to treat chronic pain by intrathecal infusion of preservative-free morphine sulfate (PF MSO_4).

The primary endpoint of the study was the accuracy of the volume of medication delivered relative to the volume programmed for delivery, as determined at the time of pump refill (i.e., delivered-to-programmed drug volume ratio). Pump refills were required monthly for the first six months post-implantation and then quarterly until the device receives market-approval. Additional refills were allowed as needed to avoid interruption of therapy.

The secondary endpoint addressed the efficacy of treatment, as measured by changes from baseline in three different assessments:

The numeric rating scale (NRS) is an 11-point scale (0-10), with 0 meaning no pain and 10 meaning the worst imaginable pain. The patient chooses a value that best describes their average pain in the previous 24 hours.

The visual analog scale (VAS) is a 100-mm line, with 0 indicating no pain and 100 indicating the worst imaginable pain. The patient marks the line at a point that indicates their current level of pain.

The Oswestry Disability Index (ODI) is a patient-completed questionnaire that gives a subjective percentage score of level of disability in activities of daily living (ADLs). Each activity is rated on a scale of 0 (no pain/limitations) to 5 (extreme pain/limitations). The index is calculated as:

ODI (%) = (Total Score / 5 x Number of Activities Assessed) x 100

Seven clinical sites participated in this study. After IRB approval was obtained,110 patients were enrolled with informed consent, as described in Table 1. Subjects completed the NRS, VAS, and ODI questionnaires at baseline (pre-implantation), monthly for the first six months post-implantation and finally at twelve months post-implantation. Data were tabulated by an independent third party (inVentiv Clinical Solutions, The Woodlands, TX).

Table 1: Enrollment by Clinical Site

Clinical Site	Location	Primary Investigators	Number of Subjects
Center for Interventional Pain Management	St. Louis, MO	Gurpreet Padda	31
Pain Institute of Tampa	Tampa, FL	John Barsa	20
Fox Chase Pain Management Associates	Jenkintown, PA	Steven Rosen	17
Center for Clinical Research	Winston-Salem, NC	Richard Rauck	16
Center for Pain Relief	Charleston, WV	Timothy Deer	16
Pain Control Network	Louisville, KY	Elmer Dunbar	7
Lowell General Hospital	Lowell, MA	Gopala Dwarakanath	3
			Total 110

RESULTS

Study Demographics

Of the 110 patients enrolled, efficacy data were analyzed for 102 patients. Eight patients were excluded from efficacy analyses because either their baseline NRS score was <4, they did not have baseline (or screening) pain/disability data, or the Prometra System was explanted due to infection prior to the first follow-up visit.

For the 102 patients included in the efficacy analyses, the most common causes of pain were post-lumbar spine surgery with pain, and intractable back pain.

As of December 3, 2008, there were a total of 45,038 days of device experience (mean 15 months, range 1-21 months), and 76 patients (75%) have completed at least 12 months of follow-up. Three patients (3%) withdrew from the study due to perceived lack of pain relief. Demographics of the study population are described in Table 2; pain history data are provided in Table 3.

RESULTS

Table 2: Demographics

Demographic	Total (*N*=102)
Gender - *N* (%)	
Male	55 (54%)
Female	47 (46%)
Age at Implant	
Mean ± SD	55 ± 13 years
Range	28-83 years
Patients with Spinal Cord Stimulators	21 (21)
Patients having Previous Pump System Replaced with Prometra System	17 (17)

Table 3: Pain History

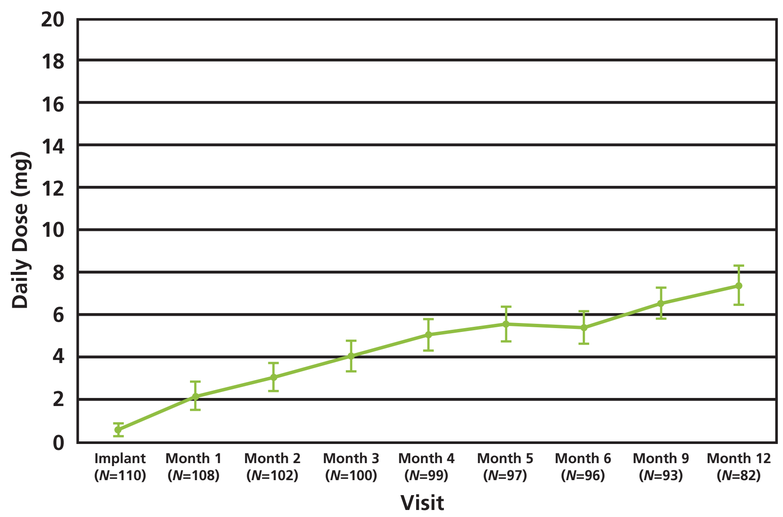
Pain History Variable	Total (*N*=102)
Duration of Pain (mean ± SD)	12.3 ± 9.8 years
Pain Category – *N* (%)	
Neuropathic	59 (58)
Nociceptive	12 (12)
Both	31 (30)
Causes of Pain* - *N* (%)	
Post Lumbar Spine Surgery with Pain	56 (55)
Intractable Back Pain	53 (52)
Arachnoiditis	23 (23)
Chronic Regional Pain Syndrome	23 (23)
Post Cervical Spine Surgery with Pain	13 (13)
Vertebral Body Compression Fractures	6 (6)
Cancer Pain	3 (3)
Post Thoracotomy Pain Syndrome	3 (3)
Other	65 (64)

* Percentages add up to greater than 100% because patients may be counted in more than one category.

Morphine Dosage

Daily programmed morphine dosage is presented in Figure 1. The increases in median daily dose from the time of implant are consistent with previous studies.[1, 2]

Figure 1: Median Daily Dose (mg) by Visit



Efficacy

Statistically significant improvements from baseline in average pain and disability (i.e., decreases from baseline in NRS, VAS, and ODI scores) were reported at each visit during the first 6 months and at 12 months. Improvements from baseline were reported by at least 61% of subjects completing 6 months of follow-up questionnaires, and at least 66% of subjects completing 12 months of follow-up questionnaires. A negative change from baseline indicates an improvement (decrease) in pain or disability due to pain.

Figure 2: Mean VAS Score by Visit

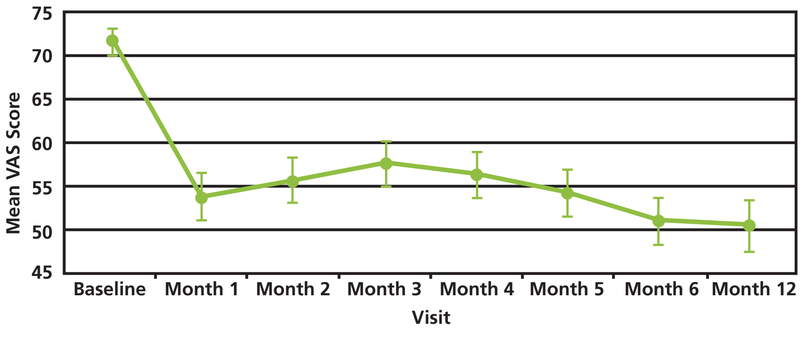
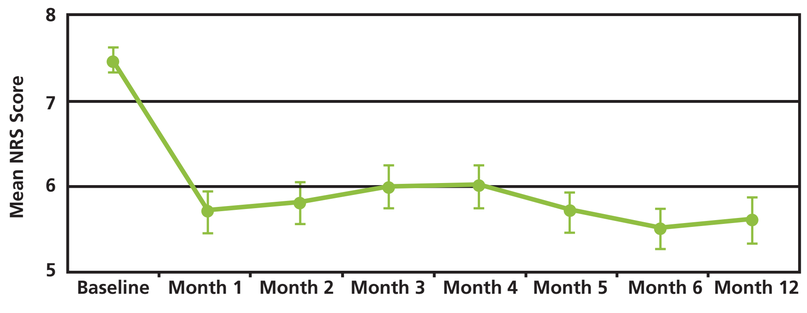
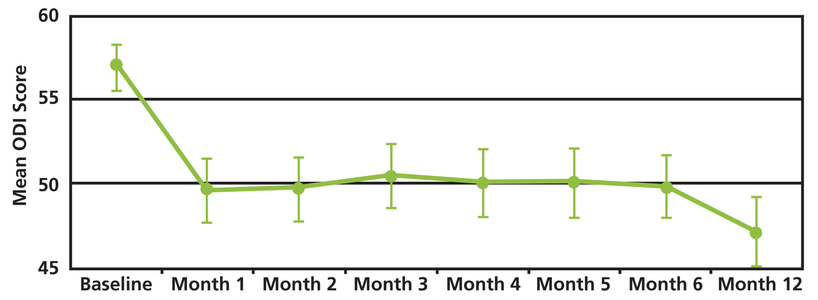


Figure 3: Mean NRS Score by Visit



RESULTS

Figure 4: Mean ODI Score by Visit



Accuracy

Of the 110 patients enrolled, accuracy data were collected from 107 patients. Three patients required explants prior to the Month 1 visit due to infections. Based on 957 refill procedures completed in 107 patients, the average accuracy of drug delivery was 97.3% ± 0.4%.[†] Accuracy is summarized in Table 5. All refill data, whether collected at required follow-up visits or additional "unscheduled" visits are included in the accuracy data presented.

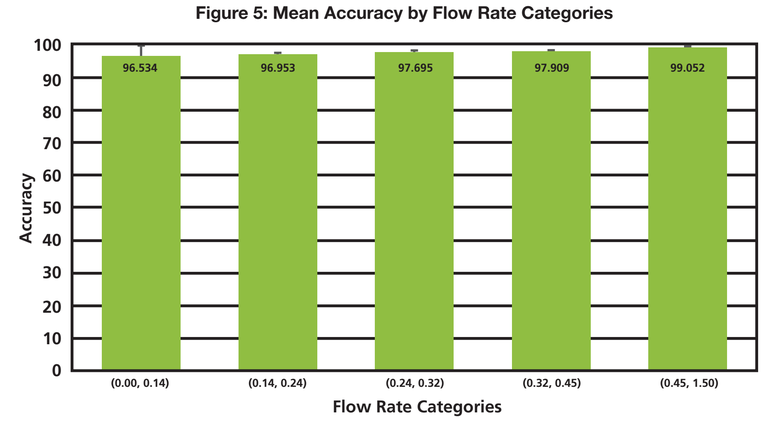
[†] Data presented as mean ± standard error.

Table 5: Summary of Accuracy

Description	Results
Number of Patients	107
Number of Refills	957
Mean	97.3%
Standard Error of the Mean	0.4%
Median	97.7%
90% Confidence Interval of Mean	***96.6 – 97.9%***

Programmed flow rates ranged from 0.0-1.5 mL/day. In order to assess accuracy as a function of flow rate, programmed rates were divided into categories with similar numbers of measurements in each group. Results for accuracy by flow rate category are presented in Figure 5. No significant differences were observed.

Figure 5: Mean Accuracy by Flow Rate Categories



DISCUSSION

Morphine delivered intrathecally via the Prometra Pump provided substantial pain relief and decreased disability scores for 12 months post-implantation. Pain relief was evident by the first visit (one month post-implantation). Only 3% of patients reported lack of pain relief that was significant enough to cause them to terminate the study, while 66% of patients reported sustained pain relief at 12 months post-implantation.

Accuracy results indicate the Prometra System had an overall mean flow rate error of less than ±3%, compared to the ±14.5% range indicated for currently marketed pumps. The accuracy results remain consistent when viewed over the range of flow rates programmed during the study. No statistically significant differences were observed.

CONCLUSION

This study shows that the new Prometra Pump System can provide effective intrathecal therapy with improved accuracy, and therefore offers the potential for improved patient outcomes through the reduced risk of under- and overdosing. The unique pump design also offers:

- reduced sensitivity to environmental temperature and pressure
- sustained accuracy at low pump volumes (i.e., throughout the entire refill interval)
- ability to program zero flow, enabling bolus delivery as an alternate therapeutic approach

REFERENCES

[1] Onofrio BM, Yaksh TL. Long-term Pain Relief Produced by Intrathecal Morphine Infusion in 53 Patients. *Journal of Neurosurgery* 72:200-209, 1990.
[2] Paice JA, Penn RD. Intraspinal Morhpine for Chronic Pain: A Retrospective, Multicenter Study. *Journal of Pain and Symptom Management* 11(2): 71-80, 1996.

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CAUTION: Investigational Device. Limited by Federal (or United States) Law to Investigational Use.