Multi-Center Evaluation of Efficacy of Morphine Sulfate infusion via the Prometra® Programmable Intrathecal Pump

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INTRODUCTION

Decreased disability and pain levels are the primary desired outcomes when treating pain patients with an implantable infusion pump. The efficacy of the new Prometra Programmable Pump System was evaluated in a prospective, multi-center, FDA-approved clinical study.

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 micro-volume 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 infusion of preservative-free morphine sulfate (MSO_4). The primary endpoint for the study was the evaluation of accuracy of drug delivery (see accompanying poster). The secondary endpoints 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). The questionnaire examines perceived level of disability in ten ADLs, with each activity 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

After IRB approval was obtained at seven clinical sites, 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).

METHODS

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

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 they had the Prometra System explanted due to adverse events 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 have been 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.

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[1] - *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)

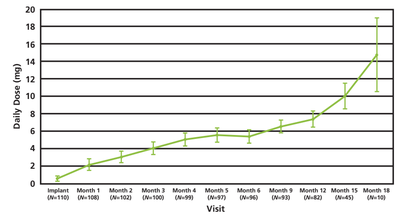
[1] Percentages add up to greater than 100% because patients may be counted in more than one category.

RESULTS

Morphine Dosage

Daily programmed morphine dosage is presented in Figure 1. Increases from implant were noted in median daily dose.

Figure 1: Median Daily Dose (mg) by Visit



Efficacy

Statistically significant improvements in 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.

Table 4 summarizes the results for the VAS, NRS, and ODI. A negative change from baseline indicates an improvement (decrease) in pain or disability due to pain. All reported changes from baseline are statistically significant (all *p* values are <0.05).

Table 4: Summary of Changes in Pain Scores and Disability Index

Visit	Efficacy Population (*N*=102) Percentage Change from Baseline VAS	Efficacy Population (*N*=102) Raw Change from Baseline NRS	Efficacy Population (*N*=102) Percentage Change from Baseline ODI
Month 1			
N	95	94	95
Mean	-25.1	-1.8	-12.1
SD	35.6	2.2	29.5
p value[2]	<0.0001	<0.0001	0.0001
Month 2			
N	92	91	92
Mean	-20.5	-1.7	-11.4
SD	38.0	2.5	29.4
p value	<0.0001	<0.0001	0.0003
Month 3			
N	89	89	89
Mean	-16.7	-1.5	-9.2
SD	39.2	2.3	28.7
p value	0.0001	<0.0001	0.0031
Month 4			
N	87	87	87
Mean	-20.4	-1.5	-10.0
SD	34.9	2.3	31.5
p value	<0.0001	<0.0001	0.0041
Month 5			
N	82	82	82
Mean	-23.1	-1.8	-9.7
SD	35.0	2.1	29.0
p value	<0.0001	<0.0001	0.0033
Month 6			
N	83	83	83
Mean	-28.4	-2.0	-10.0
SD	-34.7	2.1	26.6
p value	<0.0001	<0.0001	0.0010
Month 12			
N	59	59	59
Mean	-26.9	-1.8	-12.6
SD	32.1	2.0	27.6
p value	<0.0001	<0.0001	0.0009

[1] "Baseline" is the assessment completed on the day of implant (prior to surgery). If the assessment was not completed on the day of implant, results from the Screening assessment were used.
[2] Paired T-test

Figure 2: Mean VAS Score by Visit

Results for the VAS pain scores show that statistically significant decreases in pain from baseline were reported at each month.

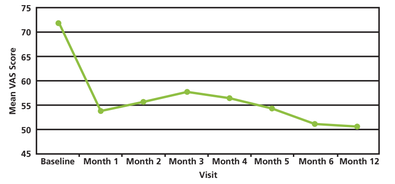


Figure 3: Mean NRS Score by Visit

Results for the NRS pain scores show that statistically significant decreases in pain from baseline were reported at each month.

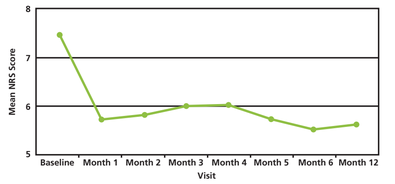
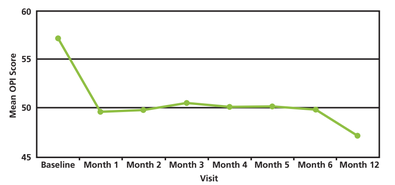


Figure 4: Mean ODI Score by Visit

Results for the ODI scores show that statistically significant decreases in disability from baseline were reported at each month.



DISCUSSION

Morphine delivered intrathecally via the Prometra Pump provided substantial pain relief and decreased disability scores for at least 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. All improvements were statistically significant from baseline. This shows excellent acceptance of this treatment modality in a group of difficult-to-treat patients. There was a trend towards increased morphine dosing consistent with tolerance, however pain scores remained low throughout the study and in fact improved with time. Data was collected in a prospective manner by a disinterested third party, as opposed to most other pump studies, which are retrospective. Data collection will continue until FDA approval.

CONCLUSION

This study shows that this newly developed and highly accurate pump is shown to give pain relief consistent with current medical practice. However, the pump's unique design may allow improved therapy in other ways, such as reduced sensitivity to temperature and pressure changes, sustained accuracy at low pump volumes, and precise dosing. The ability to program the pump to zero flow between bolus dosing may also be a significant improvement for this therapy.

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