Retrospective Study

ANALGESIC EFFECTIVENESS OF INTRATHECAL PUMP THERAPY FOR CHRONIC PANCREATITIS: A RETROSPECTIVE ANALYSIS

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Background: This retrospective study analyzed data among a single-center cohort of patients at a university hospital center designed as an Institutional Review Board (IRB)-approved retrospective chart review to assess the outcomes associated with intrathecal pump (ITP) placement in patients with severe abdominal pain from chronic pancreatitis.

Objectives: Examine ITP therapy as an alternative form of analgesia for chronic pancreatitis.

Study Design: A retrospective analysis.

Setting: The pain management department at the University of Toledo.

Methods: The primary outcomes assessed oral narcotic requirement, visual analog scale (VAS) pain scores, and the number of hospital admissions, with the outcome assessments taken pre-ITP placement and 1, 6, 12, and 24 months post-ITP placement.

Results: A total of 8 patients, with a mean age of 44.6 years, who underwent ITP placement following failed conservative therapies for abdominal pain from chronic pancreatitis were reviewed. A reduction in pain level average (VAS) was noted from pre-ITP placement (VAS = 8.38, SD = 1.49) to post-ITP placement at 1 month (VAS = 4.85, SD = 2.20, $P = 0.0127$), 6 months (VAS = 4.43,

SD = 2.50, $P = 0.0134$), 12 months (VAS = 3.67, SD = 2.36, $P = 0.0112$), and 24 months (VAS = 4.8, SD = 2.63, $P = 0.0459$). A reduction in mean hospitalizations (MH) post-ITP was noted from pre-ITP placement (MH = 9.25, SD = 11.12) to post-placement at 1 month (MH = 0, SD = 0, $P = 0.0637$), 6 months (MH = 0.125, SD = 0.33, $P = 0.1403$), 12 months (MH = 0.167, SD = 0.37, $P = 0.1502$), and 24 months (MH = 0.2, SD = 0.4, $P = 0.1457$). A reduction in mean oral morphine sulfate equivalents (MEq) occurred from pre-ITP placement (MEq = 293.98, SD = 302.99) to post-ITP placement at 1 month (MEq = 11.025, SD = 19.35, $P = 0.0369$), 6 months (MEq = 14.4, SD = 19.55, $P = 0.0578$), 12 months (MEq = 19.95, SD = 24.24, $P = 0.0542$), and 24 months (MEq = 17.64, SD = 29.38, $P = 0.0896$).

Limitations: The small sample size and the retrospective nature of this study prove to be 2 major limitations.

Conclusions: Statistically significant improvements in postoperative pain levels across all of the time intervals post-ITP, in addition to large gross reductions in MH and MEq, collectively yield promising results for ITP therapy as an alternative treatment modality for chronic abdominal pain in patients with chronic pancreatitis.

Key words: Intrathecal pump, intrathecal therapy, chronic pancreatitis, abdominal pain, chronic pain, analgesic effectiveness

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Chronic pancreatitis is a debilitating condition that can predispose a patient to nutritional deficiencies, infections, and intractable abdominal pain, all which can significantly alter the patient's wellbeing. Out of the manifesting symptoms, abdominal pain is one the major contributors to recurrent hospitalizations influencing healthcare costs (1,2). To date, the accepted treatment for chronic pancreatitis-induced abdominal pain consists of narcotic medical management (3).

Understanding the pathophysiology of neural mediated pancreatitis-associated pain has yielded numerous theories over the last several decades. Nociceptors are sensory nerve cells capable of integrating and transducing nociceptive stimuli into pain signals (4-7). Clinically, these changes manifest as allodynia, hyperalgesia, and secondary hyperalgesia, requiring a broad spectrum of modalities focusing on adequate pain control, most often via narcotic pain medication (8-10). Although effective at modulating the patient's symptoms, chronic narcotic use leaves the patient at risk for narcotic tolerance, dependence, and withdrawals. We examine and propose an alternative interventional means for treating this symptom via an intrathecal pain pump (ITP).

Thus far, there has been limited published data analyzing an effective treatment modality. A review of literature demonstrates that the traditional methods of treatment in patients suffering from chronic pancreatitis include enzyme replacement, gastric acid suppression, oral narcotics, pancreatic radiation therapy, and invasive methods including endoscopic celiac plexus block and pancreatectomy (11,12). In our literature search, we identified one retrospective study (examining 13 patients) (13), a pilot series (14), and a case report which examined an ITP as a potential treatment for chronic pancreatitis (15). There were promising results indicating the potential benefits of this treatment modality including improved analgesia and diminished narcotic dependence. We present a single-center retrospective study of the analgesic effectiveness of ITPs in the treatment of chronic pancreatitis.

METHODS

We designed a retrospective study to assess the efficacy of ITP therapy for patients who have a chronic pain syndrome secondary to chronic pancreatitis.

The study's design and protocol to review electronic medical records received Institutional Review Board approval at the University of Toledo Medical Center in Toledo, Ohio. The inclusion criteria for this study were male and female patients who were at least 18 years old, who had previously been treated with ITP therapy for chronic pancreatitis from January 1, 2010 to May 13, 2016. The exclusion criteria were patients under the age of 18 and patients who received ITP therapy for any condition other than chronic pancreatitis. All of the patients identified had been referred to the pain management department at the University of Toledo for chronic pain management after having failed multiple other therapies. Following evaluation, each included patient underwent a successful ITP trial, followed by permanent ITP implantation. There were no ITP trial failures, as all of the patients identified as candidates for an ITP trial for chronic abdominal pain secondary to chronic pancreatitis had a successful pump trial leading to implant. The choice of the intrathecal medication used was selected at the discretion of the provider, with initial dosing based off of the dose that provided greater than 50% analgesia during each patient's pump trial.

Post-ITP implant, patients were weaned off oral opioids with a 20% reduction from pre-implant oral morphine sulfate equivalents (MEq) made weekly with the goal of discontinuation, if possible, within 1 month post-implant. Non-opiate oral medications were not adjusted pre- or post-implant. Additionally, the intrathecal drug dose was increased incrementally as needed during the follow-up visits 10–20% at a time with the goal of at least 50% analgesia.

The outcomes were defined to assess the degree of analgesic effectiveness in chronic pancreatitis post-ITP placement, with the primary outcomes defined as pre- and post-ITP oral narcotic requirement (standardized through oral morphine sulfate equivalents in milligrams, calculated using drug, dosing, and frequency), pre- and post-ITP visual analog scale (VAS) pain scores on a 0–10 scale, and the number of hospital admissions pre-ITP and post-ITP. The outcome assessments were taken using records from regularly scheduled visits (pre-ITP placement and 1, 6, 12, and 24 months post-ITP placement).

Statistical analyses were performed using SPSS Version 22.0 (IBM Corporation, Armonk, NY). Aside

from reporting median and/or mean + standard deviation, a paired 2-tailed t-test was performed to assess for statistical significance, comparing mean hospitalizations (MH), VAS scores, and MEq respectively, pre-ITP to 1, 6, 12, and 24 months post-ITP, with significance defined as $P < 0.05$.

RESULTS

We treated 8 patients (5 men and 3 women), with the mean age being 44.6 years old (SD = 8.85), with refractory epigastric pain from chronic pancreatitis (etiologies: chronic alcoholic intake ($n = 3$), pancreatic obstruction ($n = 3$), interferon therapy for hepatitis C ($n = 1$), and pancreatic pseudocyst ($n = 1$). Each patient underwent oral opioid therapy, endoscopic procedures, and celiac plexus blocks. When these interventions failed to provide adequate relief, ITP therapy was offered.

We evaluated the VAS scores, MEq, and MH from pre-ITP placement to 1, 6, 12, and 24 months post-ITP placement. A reduction in the pain level average (VAS score) was noted (Fig. 1a) from pre-ITP placement (VAS = 8.38, SD = 1.49) to post-ITP placement at 1 month (VAS = 4.85, SD = 2.20, $P = 0.0127$), 6 months (VAS = 4.43, SD = 2.50, $P = 0.0134$), 12 months (VAS = 3.67, SD = 2.36, $P = 0.0112$), and 24 months (VAS = 4.8, SD = 2.63, $P = 0.0459$). A paired 2-tailed t-test showed that when compared to pre-ITP placement VAS scores, there was a statistically significant decrease in VAS scores for every time interval. Only one patient reported worsening pain over the first 6 months following ITP placement, followed by 33% pain relief from a VAS score of 6 pre-ITP placement to a VAS score of 4 at 12 and 24 months post-ITP assessments. All of the other patients maintained lower post-ITP VAS scores in every time interval for the duration of follow-up. Two patients reported 100% relief following ITP placement and one maintained 100% relief through the end of the 24 month follow-up period.

Each patient received any one of the following intrathecal medications: hydromorphone (0.2403 - 3.447 mg/day) with bupivacaine (0.2403 - 3.447 mg/day) { $N = 5$ }, hydromorphone (0.798 - 1.262 mg/day) { $N = 1$ }, hydromorphone (1.491 - 6.563 mg/day) with bupivacaine (1.491 - 6.563 mg/day) and clonidine (10.941 - 32.81 mcg/day) { $N = 1$ }, or morphine (0.96

mg/day - 1.15 mg/day) { $N = 1$ }. During follow-up, if a patient reported less than 50% pain relief, a decision was made to make 10–20% dose increases with the overall goal of 50% overall pain relief.

In the 24 months prior to ITP placement, 6 out of 8 patients had been admitted to the hospital for intractable abdominal pain secondary to chronic pancreatitis. A reduction in MH post-ITP (Fig. 1b) was noted from pre-ITP placement (MH = 9.25, SD = 11.12) to post-ITP placement at 1 month (MH = 0, SD = 0, $P = 0.0637$), 6 months (MH = 0.125, SD = 0.33, $P = 0.1403$), 12 months (MH = 0.167, SD = 0.37, $P = 0.1502$), and 24 months (MH = 0.2, SD = 0.4, $P = 0.1457$). A paired 2-tailed t-test showed that when compared to pre-ITP placement MH, there was no statistically significant ($P < 0.05$) decrease in MH in any time interval, despite obvious decreases in MH from 9.25 pre-ITP placement to between 0 and 0.167 in post-ITP placement intervals. In the 24 month follow-up period, only 2 patients were admitted a combined 3 times for pain control related to chronic pancreatitis.

The mean MEq were as follows (Fig. 1c): pre-placement (MEq = 293.98, SD = 302.99), 1 month (MEq = 11.025, SD = 19.35, $P = 0.0369$), 6 months (MEq = 14.4, SD = 19.55, $P = 0.0578$), 12 months (MEq = 19.95, SD = 24.24, $P = 0.0542$), and 24 months (MEq = 17.64, SD = 29.38, $P = 0.0896$). A paired 2-tailed t-test showed that when compared to pre-ITP placement MEq, there was only a statistically significant ($P < 0.05$) decrease in oral MEq at 1 month post-ITP placement, despite the obvious gross reductions in MEq across all of the follow-up intervals. Following ITP placement, 5 patients required no oral opioids and only 3 patients required oral narcotics in the follow-up post-ITP intervals. These 3 patients all had significant dose reductions of oral narcotics while also having gross reductions in VAS scores during the follow-up periods.

DISCUSSION

We present a single-center retrospective analysis of 8 patients who underwent ITP therapy for chronic severe, intractable abdominal pain which had failed prior conservative treatment regimes. In our primary outcome analysis, we analyzed the VAS pain scores, MH, and MEq, and used mean reductions in 1, 6, 12,

Fig. 1. A) VAS score, B) MEq, and C) MH from pre-ITP placement to one, six, twelve, and twenty-four months post-ITP placement.

and twenty-four month post-ITP implant intervals as well as a paired 2-tailed t-test to determine significance.

There was a statistically significant reduction ($P < 0.05$) in the VAS scores for every time interval. This encompassed a 41.79% and 42.72% reduction in the average VAS score from pre-ITP placement to one month and twenty-four months post-ITP placement respectively, with two patients reporting 100% relief immedi-

ately at one month post-ITP. The greatest mean VAS reductions from pre-ITP levels were most apparent at one month post-ITP, elucidating the immediate efficacy of ITP therapy. We attribute worsening pain over the first six months following ITP placement for one patient to hyperalgesia; however, this period was followed by 33% pain relief thereafter through twenty-four months post-ITP. There were differences in the type and combination of intrathecal therapy used, the dose used, and the timing of dose escalation for each patient. These factors may have had influenced the results, however, are not uncommon practices in general ITP management and maintenance across institutions (16-20).

The gross reductions in MH from 9.25 in the twenty-four months pre-ITP placement to between 0.00 and 0.167 in post-ITP intervals we attribute to better outpatient pain control from ITP therapy, despite these results not being statistically significant. The lack of statistical significance most likely is due to the low sample size and large variance in MH pre-ITP placement (MH = 9.25, SD = 11.12). Abdominal pain in the setting of chronic pancreatitis is a significant symptom and challenge for clinical practitioners. Pancreatitis-associated pain is present in 90% of chronic pancreatitis patients and is a leading cause of hospitalization, responsible for increased healthcare costs for the patient and an increased burden on hospital staff (9). Lower utilization of inpatient resources is a major goal in the treatment of chronic pancreatitis, with a majority of admissions due to uncontrolled abdominal pain. These admissions put a strain on the healthcare system that can possibly be prevented through improved outpatient pain control. The gross reductions in MH observed here, as well as the statistically significant reductions in VAS scores in our study show that ITP therapy for chronic pain control in chronic pancreatitis has promising prospects for preventing inpatient admissions for uncontrolled chronic pain.

Oral narcotic dependence often becomes a problem for both patients and practitioners because dose escalation, narcotic tolerance, dependence, and withdrawal become significant issues in the chronic management of pain with oral opioids. Our final primary outcome assessing oral narcotic utilization pre- and post-ITP, as measured through MEq showed a 96.25% dose reduction one month post-ITP implant (P

= 0.0396) and a 94.00% dose reduction 24 months post-ITP implant ($P = 0.0896$). The dose reduction was only significant at 1 month post-ITP, despite the observed large gross reductions in dose which was maintained at 6, 12, and 24 months post-ITP. This lack of significance again we attribute to the low sample size and large variance among MEq pre-ITP (MEq = 293.98, SD = 302.99). However, 5 patients required no oral opioids post-ITP, elucidating the efficacy of ITP therapy in both controlling chronic pain and the quick, effective discontinuation of oral opioids in chronic opioid users.

ITP therapy for patients with severe, intractable chronic pain related to chronic pancreatitis has been previously studied. We found similar results in our study as compared with previous studies demonstrating ITP as an alternative treatment modality to both narcotics and surgical intervention (13-15). One recent study comparing ITP therapy with total pancreatectomy and islet cell transplant showed that in addition to achieving similar levels of pain control, compared with patients undergoing total pancreatectomy for chronic pancreatitis, there was a further benefit of preserved glucose and insulin metabolism in the patients who underwent ITP therapy (13).

Additionally, there is limited data assessing the long-term efficacy and complications associated with ITP therapy in patients with chronic pancreatitis. The most common complications typically reported from ITP therapy include meningitis, catheter migration, CSF leak, and ITP leak (18,21). In our study, there were no major complications related to ITP placement reported.

CONCLUSION

Chronic pancreatitis-induced pain is the foremost symptom resulting in patient distress. We found statistically significant improvements in postoperative pain levels across all of the time intervals post-ITP. Additional large gross reductions in MH and MEq collectively yield promising results for ITP therapy as an alternative treatment modality for chronic abdominal pain in patients with chronic pancreatitis. The small sample size and retrospective nature of this study were 2 major limitations of this study. Additional larger scale studies are needed to further assess both the efficacy and potential risks of ITP therapy for chronic pancreatitis.

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