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Review Article

Treatment of Medically Refractory Cancer Pain with a Combination of Intrathecal Neuromodulation and Neurosurgical Ablation: Case Series and Literature Review

J. Nicole Bentley, MD,* Ashwin Viswanathan, MD,†‡ William S. Rosenberg, MD,§‡ and Parag G. Patil, MD PhD*‡¶

Departments of *Neurosurgery and ¶Anesthesiology, University of Michigan, Ann Arbor, Michigan; †Department of Neurosurgery, Baylor College of Medicine, Houston, Texas; ‡Cancer Pain Research Consortium, Kansas City, Missouri; §Center for the Relief of Pain, Midwest Neuroscience Institute, Kansas City, Missouri, USA

Reprint requests to: Parag G. Patil, MD, PhD, Department of Neurosurgery, University of Michigan, 1500 East Medical Center Drive, SPC 5338, Ann Arbor, MI 48109-5338, USA. Tel: 734-936-9579; Fax: 734-936-9294; E-mail: pgpatil@umich.edu.

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Abstract

Objective. Up to 90% of patients with advanced cancer experience intractable pain. For these patients, oral analgesics are the mainstay of therapy, often augmented with intrathecal drug delivery. Neurosurgical ablative procedures have become less commonly used, though their efficacy has been well-established. Unfortunately, little is known about the safety of ablation in the context of previous neuromodulation. Therefore, the aim of this study is to present the results from a case series in which patients were treated successfully with a combination of intrathecal neuromodulation and neurosurgical ablation.

Design. Retrospective case series and literature review.

Setting. Three institutions with active cancer pain management programs in the United States.

Methods. All patients who underwent both neuroablative and neuromodulatory procedures for cancer pain were surveyed using the visual analog scale prior to the first procedure, before and after a second procedure, and at long-term follow-up. Based on initial and subsequent presentation, patients underwent intrathecal morphine pump placement, cordotomy, or midline myelotomy.

Results. Five patients (2 male, 3 female) with medically intractable pain (initial VAS = 10) were included in the series. Four subjects were initially treated with intrathecal analgesic neuromodulation, and 1 with midline myelotomy. Each patient experienced recurrence of pain (VAS ≥ 9) following the initial procedure, and was therefore treated with another modality (intrathecal, N = 1; midline myelotomy, N = 1; percutaneous radiofrequency cordotomy, N = 3), with significant long-term benefit (VAS 1–7).

Conclusion. In cancer patients with medically intractable pain, intrathecal neuromodulation and neurosurgical ablation together may allow for more effective control of cancer pain.

Key Words. Cancer Pain; Intrathecal; Ablation; Surgery

Introduction

Many cancer patients suffer from intractable pain, with an increasing incidence as the disease progresses [1]. An estimated 60% to 90% of patients experience significant pain in the terminal stages [2–6]. With the success of intrathecal (IT) opioids and other neuromodulatory therapies, such as spinal cord stimulation, ablative procedures are now less commonly used [7]. Ablative therapies for cancer include cordotomy, myelotomy, sympathectomy, peripheral neurectomy, dorsal rhizotomy and ganglionectomy, dorsal root entry zone lesioning, and others [7,8]. Among these, two of the most commonly indicated procedures are the cordotomy and myelotomy. Cordotomy was first described in 1912 by Spiller and Martin as an open procedure [9], and has evolved into an image-guided percutaneous procedure with low morbidity [10–12]. Indicated for patients with refractory unilateral pain, this technique introduces a lesion into in the rostral cervical spinal cord for interruption of ascending spinothalamic tract fibers. In addition to its safety profile, it is also associated with short hospitalizations and relatively low costs [13]. Similarly, the midline myelotomy has low morbidity, and is performed either percutaneously or via an open laminectomy. It is indicated for midline abdominal or pelvic pain, typically in the setting of visceral malignancy, and results in interruption of dorsal crossing fibers of the spinothalamic tract [13,14]. Intrathecal therapy, first introduced in humans in 1979 [15], has therapy has proven to be a highly effective treatment option for patients with opioid-responsive pain that require increasing doses or experience intolerable side effects. IT medication delivery allows 100-fold greater potency than orally administered medications, and has a broader therapeutic range due to lowered potential for systemic side effects [16,17]. In part due to these reasons, the use of neuroablation has declined in recent years [18].

Despite the multiple available treatments for pain control and the existence of well-established guidelines [19], undertreatment of cancer pain remains in the neighborhood of 50% [20]. In addition, a subset of patients continue to experience refractory pain after optimization of oral and intrathecal medications [21], but guidance in choosing further therapies is lacking. Although IT opioids and neurosurgical ablation have been well-described individually, with published series exploring the outcomes of patients treated with either neuromodulation [22–25] or surgical ablation [10,26–29], little is known about the potential application of both modalities together in individual patients. but not both. In this case series, we report 5 patients with medically intractable cancer pain in whom a second interventional modality proved successful after the other interventional modality failed. The series illustrates the potential efficacy of a multi-modal interventional approach to cancer pain, performed sequentially, when other medical therapies have failed.

Materials and Methods

Patient Selection

All data collection was performed with the approval of, and in accordance with Internal Review Board (IRB) protocols at each of the participating institutions. All patients without exception who underwent both neuroablation and intrathecal drug delivery for cancer pain between January 2011 and December 2013 were selected for this retrospective review. A total of five patients were identified from the three participating institutions. For opioid-responsive patients, IT therapy was typically selected as the initial treatment. In response to a return of pain, or the extension of pain to a new area, patients underwent a second, adjunctive procedure. For those with unilateral pain, PRFC was chosen, and those with bilateral or midline pain underwent MM. Visual analog scale (VAS) scores were assessed pre-operatively, immediately post-operatively, and at long-term follow-up. Cases were also assessed for any complications.

Neuromodulation and Neurosurgical Techniques

IT catheter and subcutaneous pump placement, MM, and PRFC were all performed using standard surgical techniques, which have been previously described [30–33]. Briefly, intrathecal pump placement involves percutaneous introduction of a catheter in a procedure similar to lumbar puncture. The catheter is tunneled to the abdomen where it is attached to a subcutaneous medication reservoir. Level of catheter placement is typically several segments above the level of pain to ensure adequate coverage [31]. Cordotomy is also frequently performed percutaneously, with needle localization at C1-2 level under fluoroscopic or CT-guidance. The needle trajectory is towards the anterolateral quadrant of the spinal cord on the contralateral side, at least several segments above the level of pain where spinothalamic tract fibers have crossed [34]. Midline myelotomy may be performed open or percutaneously, and is designed to interrupt of dorsal crossing fibers of the spinothalamic tract by making a small incision. It is typically performed several levels above the level of pain to ensure coverage [14,32].

Results

In our series, there were 2 male patients and 3 female patients. Subjects ranged in age from 16 to 72 years, and were diagnosed with commonly occurring cancers (renal carcinoma, N = 1; non-small cell lung cancer, N = 2; rectal carcinoma, N = 1; and melanoma, N = 1). Preoperative VAS scores were 10 out of 10 in all 5 patients. Table 1 presents a summary of patient VAS scores over time.

Case Presentations

Patient 1

Patient 1 was a 72-year-old woman with renal cell carcinoma. The patient had disseminated bony metastases

Table 1 Progression of VAS scores in a multicenter series of cancer-pain patients treated with IT and ablative therapies

Patient No.	Age (yrs), Sex	Diagnosis	Initial VAS Score	First Procedure	Pre-Procedure VAS Score	Second Procedure	Postoperative VAS Score	Long-Term VAS Score (mos)
1	72, F	Renal	10	IT pump	9	Cordotomy	0	1 (3)
2	51, M	Rectal	10	IT pump	9	Cordotomy	4	4 (3)
3	16, F	Melanoma	10	Myelotomy	9	IT pump	7	7 (3)
4	64, M	NSCLC	10	IT pump	9–10	Cordotomy	0	1 (9)
5	71, M	NSCLC	10	IT pump	10	Myelotomy	3–4	4 (6)

IT = intrathecal; NSCLC = non-small cell lung cancer; VAS = visual analog scale.

and presented with refractory pain in the pelvis, sacrum, and buttocks, with an intial VAS pain score of 10. She underwent IT pump placement with the catheter tip at the superior endplate of L1, with a dosage of morphine 2 mg/day and bupivacaine 0.5% at 4 mg/day. She initially responded with a VAS score of 0, and IT neuromodulation continued to control her sacral and right hip pain until a pathological fracture of the right iliac bone and right anterior acetabulum considerably increased her pain. IT medications were titrated, with increases of morphine to 5 mg/day and bupivacaine to 10 mg/day. She subsequently rated her pain at VAS 9. As the pain was unilateral on the right, a left PRFC was performed, with complete pain relief (VAS 0). Analgesia was maintained at VAS ≤ 1 until she expired 3 months after the PRFC procedure.

Patient 2

Patient 2 was a 51-year-old male with rectal cancer and metastatic disease to the thoracic spine and pleura, causing refractory upper chest wall pain at approximately T6-8, with VAS pain score of 10. The patient underwent IT pump placement with a catheter tip at T8, and he received hydromorphone 2.65 mg/day and bupivacaine 5.3 mg/day. His pain initially improved to a 9, and IT medication doses were subsequently increased to 5.49 and 13.74 mg/day, respectively, and ziconotide 3.29 mg/day was added. Despite the increased dosage, the patient's pain remained at VAS 9. To improve his pain control, a right-sided PRFC was performed. The patient experienced an immediate decrease in chest pain, no longer required IT boluses, and was weaned off all oral pain medications. He continued to receive hydromorphone 0.5 mg/day, bupivacaine 1.25 mg/day, and ziconitide 0.4 mcg/day via the IT pump. Pain at three month follow-up was rated as VAS 4. The patient was then transferred into hospice care.

Patient 3

Patient 3 was a 16-year-old female with a history of melanoma and metastases to the small intestine. Due to intractable abdominal pain at VAS 10, she was admitted to the intensive care unit and a dexmedetomidine infusion was administered along with maximal opioid therapy. The pain persisted. A percutaneous MM (see [32] for detailed technical description) was performed was performed at the T5 level. The dexmedetomidine infusion was halted and the patient reported VAS 3 pain. Two months following the MM procedure, her pain returned to VAS 9. The patient then underwent IT pump placement with a catheter tip at T10. IT doses initially were hydromorphone 1.2 mg/day and bupivacaine 1.2 mg/day. This was increased to hydromorphone 2.6 mg/day and bupivacaine 2.6 mg/day. Following IT pump placement and titration, the patient reported VAS 7 pain at 3-month follow-up.

Patient 4

Patient 4 was a 64-year-old male with non-small cell lung cancer who had severe right-sided chest pain secondary to chest wall metastases. After chemoradiation and maximal systemic opioids, his pain remained at VAS 10. Initially, an IT pump was placed with the catheter tip at T6. Following the procedure, the patient was started on morphine and bupivacaine. Pain remained at VAS 9-10, and hydromorphone was attempted instead. Clonidine was also added. Analgesic doses were increased to the point of paraparesis and urinary retention, up to a maximum dose of hydromorphone 3,425 mcg/day and bupivacaine 20.549 mg/day. Therefore, a left PRFC was performed resulting in immediate and complete resolution of the right chest wall pain. IT dosage was decreased by 75%. Later, following development of new, opiate-responsive left-sided pain due to a small metastatic lesion, IT dosage was increased. His pain remained at VAS ≤ 1 until his death 9 months after PRFC.

Patient 5

Patient 5 was a 71-year-old male who presented with chest wall pain that extended to the top of the shoulder and lower neck, mechanical low back pain, and a left apical pulmonary mass. He was diagnosed with non-small cell lung cancer and was found to have metastatic sacral lesions producing low back pain. Despite radiotherapy and escalating opioid dosage, he continued to have VAS 10 pain that inhibited weight-bearing and upright standing. An IT pump was implanted several segments above his pain, with the catheter tip at C4, and he received

hydromorphone and bupivacaine, which completely alleviated his chest wall pain. Doses were increased, however, he continued to have intractable midline sacral pain, and therefore underwent open myelotomy at T9-10, resulting in 70–80% relief of pain (VAS 3–4), allowing sitting, standing, and ambulating. He continued to experience stable pain relief with improved quality of life until his death 6 months later.

Discussion

Cancer pain arises from various sources and is mediated by diverse mechanisms. The direct effect of tumor invasion into bones, soft tissues, or obstruction of hollow viscera accounts for 75% of all cancer pain [5]. Chemotherapy and radiation may also result in painful fibrosis or myopathies, and procedural pain from surgical resection, venipuncture, or bone marrow aspirations is also common causes [35,36]. Incidence and severity of cancer pain has been correlated with degraded functional ability and diminished quality of life. In a 10-year prospective study of 2,266 cancer patients, Zech et al. [37] reported that 12% of patients reported "severe," "very severe," or "maximal" pain greater than 30% of the time, despite medical management. Cleeland et al. [38] reported that inadequate pain control resulted in interference with work, relationships, enjoyment of life, and other activities of daily living. While cancer patients contend with the many medical issues surrounding their primary diagnosis, uncontrolled pain significantly limits their overall quality of life. In 1986, the World Health Organization (WHO) published a now well-established guideline for the treatment of cancer pain [39].The WHO recommends a 3-step ladder approach, with treatment progressing from non-opioid analgesics to mild oral opioids, then to strong oral opioids. The stated goal of the WHO guidelines has been to provide relief from pain "to the patient's satisfaction, so that [they] may function effectively and eventually die free from pain" [39].

However, due to various reasons, it is estimated that only half of cancer patients are treated according to the guidelines, leaving 50% of cancer patients undertreated [20,40]. In addition to undertreated patients, 10% of cancer patients will continue to have pain even with optimal medical therapy [41]. With the number of new cancer diagnoses per year estimated to approach 15 to 17 million worldwide in 2020, pain in this medically intractable population represents a significant public health concern [42]. Even by the most optimistic estimates, assuming a low incidence of terminal cancer pain (60%), full guideline implementation, and 90% treatment success, almost 1 million patients worldwide are expected to suffer from severe pain that fails to respond to oral medications [43].

For these patients with moderate-to-severe and medically intractable cancer pain, both IT-targeted drug delivery and neurosurgical ablation are treatment strategies with demonstrated safety and efficacy [13,44]. Many other procedures are in use, with varying success. Among these are peripheral nerve or plexus anesthetic blockade, chemical neurolysis, and spinal cord stimulation (SCS). Each of these has its own risk-benefit profile, and have been variable successful. Recurrence of pain occurs frequently, and is a significant factor in determining surgical candidates for these procedures. Serial attempts have few proponents, as this increases the rate of complication from damage to surrounding tissues, neurologic deficit, and development of new pain. However, they as relatively straightforward and have low associated morbidity, and therefore, continue to be useful adjuncts and worthy of trying before moving to more permanent approaches [45].

Recently, comprehensive consensus guidelines have emerged for the treatment of cancer pain with IT neuromodulation [44]. In malignancy, it is generally more commonly performed than SCS due to the presence of well-designed randomized control trials showing its effectiveness when used in conjunction with maximal medical management [18]. In a randomized controlled comparison of the two, both SCS and IT therapy provided pain reduction, though there was a trend toward greater pain relief with IT therapy [46]. Administration of IT opioids is the most extensively studied neuromodulatory intervention for chronic pain, first described in 1979 by Wang et al. [15], who found a potent analgesic effect with serial bolus dosing administered to the subarachnoid space. In a randomized controlled trial, Smith et al. [18] reported that 84.5% of patients experienced successful pain relief with the use of IT pumps, in comparison to 70.8% of patients receiving comprehensive medical management ($P = 0.05$). Additionally, rates of cognitive and systemic toxicities were far lower among patients receiving IT therapy. IT therapy is currently indicated for use in patients with intractable nociceptive and neuropathic pain who respond well to oral opioids, but despite increased and optimized doses, continue to have pain [44]. In addition, it is indicated for use in patients for whom oral therapy is associated with intolerable systemic side effects, such as nausea, pruritus, urinary retention, or respiratory depression. Currently, the only FDA-approved analgesic medications for IT pumps are morphine and ziconitide However, according to consensus guidelines published in 2007, monotherapy with either morphine, hydromorphone, or ziconitide are acceptable first-line treatments [44]. Failure to adequately control pain with these medications warrants use of second-line therapies, which includes replacement of a first-line medication with fentanyl, or addition of either bupivacaine or clonidine to ziconitide. Third-line therapy warrants use of ziconitide with a second-line therapy, or clonidine monotherapy. Fourth-line treatments include addition of sufentanil, ropivicaine, buprenorphine, midazolam, meperidine, or ketorolac, octreotide, gabapentin, or investigational medications [44].

Though these guidelines note that third-line pharmacological therapies and beyond have limited clinical efficacy data, no mention is made of the addition of neuroablative

therapies for synergistic pain control. Although IT targeted drug delivery and neurosurgical ablation are well-described and effective options, poor response to these procedures and/or recurrence of pain are well-recognized possibilities. Recommendations on how best to proceed after failure of one of these treatments are unavailable to treating physicians [33,47]. While it may seem that failure of an invasive procedure precludes further surgical intervention, our results illustrate a variety of patient conditions and presentations in which a combination of IT therapy and ablation was used effectively and safely. Based on our results, earlier intervention with these may provide immediate and durable pain control, decreasing the amount of time necessary for medication titration. This is particularly well-illustrated in patients 1, 2, 4, and 5, who initially had an IT pump placed and underwent medication titration with additional second- and third-line therapies, but continued to have refractory pain. Rather than continue down the avenue of medication trial-and-error, neuroablation resulted in excellent pain relief, decreasing the need for IT analgesia.

Before considering the initial surgery a treatment failure, physicians should adopt a methodical approach to ensuring optimal therapy is being delivered. Development of pain in a new area should prompt evaluation for new metastases. As illustrated in Patient 4, some lesions may be opioid-unresponsive or persist due to opioid tolerance, while others in the same patient respond well. Though the pathophysiologic mechanism of this disparate response is not understood, we achieved good control of pain by progressing along the same algorithm, beginning with the most conservative approach of oral/epidural medication titration. If a pump is implanted, it is important to interrogate it in the initial evaluation. X-rays should be obtained to ensure that failure is not due to catheter migration, breakage, or kinks, and occasionally nuclear medicine studies are indicated to evaluate for obstruction. The catheter tip is generally optimally placed several segments above the level of pain, though in the authors' experience with IT pumps and bolus IT trials, pain relief is achieved even when the tip is at or a couple of segments below the site of pain. The ablative procedures are most strongly indicated for pain from malignancy, as pain recurrence is a significant concern, though long-term relief has been reported for up to 40 years with cordotomy [48]. For cordotomy, return of pain is seen in about 50–60% of patients at one year [34], and in MM, return of pain was seen in 30% at 6 months [14].

In addition, there are no clear-cut guidelines for which initial therapy is best, and some outcomes may be unpredictable and surprising, as in our third and fifth patients. In the third case, the patient seemed an excellent candidate for initial MM due to the inadequate response to oral and IV analgesics and well-localized midline abdominal pain. However, failing this, subsequent IT implantation provided much more relief, begging the question of whether an IT pump would have been a better first choice. In retrospect, this is a valid question, but would not have been predicted based on her previous clinical response. Though this case may present clinical frustration at the difficulty in patient selection, it highlights the need for evaluation by specialists familiar with the many available modalities. In the case of the fifth patient, it is worthy to wonder if both treatments should have been done simultaneously, as his pain was

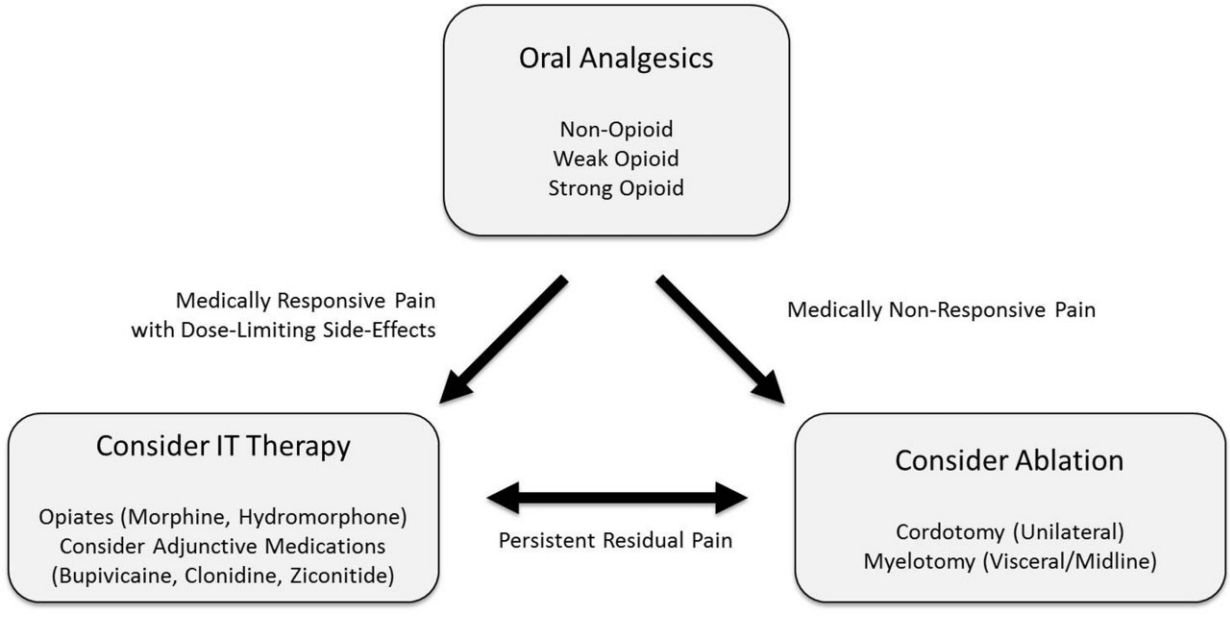

Figure 1 Proposed treatment algorithm for the approach to management of cancer patients with medically refractory pain.

widely disparate. IT pump was initially placed as the most conservative approach, with the hope of covering the whole extent of his pain. However, it was not until some time later that this was deemed a failure. As so many patients respond well to IT therapy, it is usual practice to trial this and ensure it is optimized before subjecting patients to a second procedure.

In our series, no complications from neurosurgical ablation or IT pharmacotherapy were observed. Operative time, hospital length of stay, and postoperative courses were as expected for these operations. Furthermore, whether ablation preceded neuromodulation or vice-versa, all patients experienced some benefit. Based on our results and the previously described WHO approach, we recommend consideration of an approach to persistent refractory cancer pain as illustrated in Figure 1, though consideration should also be given to SCS, neurectomy, or nerve blockade in appropriately selected individuals.

We fully acknowledge that our small, retrospective series provides only a first step to develop a broader consensus and evidence-based paradigm incorporating medical management, IT neuromodulation, and neurosurgical ablation. Among three institutions, five patients underwent both neuromodulatory (IT pump placement) and neuroablative (myelotomy or cordotomy) for cancer pain control. While this may be due to the rarity of the occurrence of persistent pain in the setting of an initial procedure and successful medical management thereafter, it may also be due to a hesitancy to refer patients for secondary procedures. A much larger cohort of cancer pain patients are needed to fully understand the safety and efficacy of this treatment algorithm. However, in order to provide treatment options for this group of patients, we advocate for a persistent approach, combining medical, modulatory, and ablative modalities.

Conclusions

Medically intractable cancer pain presents an enormous challenge, robbing cancer patients of quality of life in the terminal stages of their disease. In an effort to expand upon the current guidelines for management of these patients, we have presented a series of patients in whom a combination of neurosurgical modulation and ablation were both safe and efficacious.

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