Neuraxial Infusion in the Management of Cancer Pain

Pain due to malignancy can be controlled through simple means in most patients. In certain refractory cases, however, the chronic delivery of analgesics to the epidural or subarachnoid space may be appropriate. This review

ABSTRACT: Pain due to malignancy can be controlled through simple means in most patients. In certain refractory cases, however, the chronic delivery of analgesics to the epidural or subarachnoid space may be appropriate. This review will discuss criteria for patient selection for neuraxial drug delivery, the technologic systems available for neuraxial drug delivery, and criteria for selection of the appropriate technology in the individual patient. [ONCOLOGY 13(Suppl 2):30-36, 1999]

Introduction

A review of the various systems available for neuraxial infusion must be preceded by a very basic question: “When and in whom is it practical to use these neuraxial drug delivery systems?”

The majority of patients with cancer pain can be effectively treated with oral medication. The World Health Organization (WHO) analgesic ladder consists of a hierarchy of oral pharmacologic interventions designed to effectively treat pain of increasing magnitude.[1] The WHO paradigm presents a framework for the rational use of oral medication before consideration is given to the application of other techniques of drug administration.

Approaches to Managing Pain

![Paradigm for the Management of Cancer Pain](image)

The Practice Guidelines for Cancer Pain Management[2] from the American Society of Anesthesiologists provides an evidence-based paradigm for the use of neuraxial drug delivery systems (Figure 1). Oral medications should initially be used in the management of most types of cancer pain. When analgesia, with or without acceptable side effects, can no longer be achieved, or oral administration is no longer viable because of the presence of intolerable side effects or the inability of the patient to swallow or absorb medication, an alternate route of administration should be employed. Transdermal fentanyl may be used in patients with stable pain states who are either noncompliant with oral medications or unable to swallow or absorb medication. Subcutaneous or intravenous administration may be employed in patients with dynamic pain states who have a frequent need for “rescue” dosing for breakthrough pain, or in patients who are unable to swallow or absorb opioids and may benefit from a continuous infusion.

In general, neuraxial drug infusions should be considered when adequate analgesia cannot be achieved with systemic methods of drug delivery or when intolerable side effects occur. Neuraxial drug delivery should be used:

1. when severe pain cannot be controlled with systemic drugs because of dose-limiting toxicity;
2. when there is immediate need for a local anesthetic (some types of neuropathic pain);
3. after failed neuroablation; or
4. when patient preference indicates its use.

Similar to neuraxial drug delivery, neuroablative techniques should be considered when systemic therapies have failed to provide adequate analgesia or adverse effects are intolerable. Neuroablative techniques can be used early in the natural history of cancer pain in the presence of focal somatic lesions (e.g., rib metastases) and in certain visceral (e.g., pancreatic cancer) or neuropathic (e.g., craniofacial) pain states. Neuroablation may be employed after failure of neuraxial drug administration, if appropriate.

Neuraxial drug delivery (neuroablative therapies, also) should not be used in unmotivated or noncompliant individuals, in persons who do not possess the prerequisite cognitive functioning to understand the risks and benefits, or when appropriate logistical systems do not exist. Thus, use of neuraxial drug delivery systems does not merely imply the ability to perform sophisticated technologic procedures. Appropriate patients must be selected and resources and personnel must be available to respond to patients on an as-needed, around-the-clock basis. This implies the establishment of an office or network with professional support and integration of home care into the organizational construct for provision of care.

**Technologic Systems**

**TABLE 1**

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<th>Neuraxial Drug Delivery Systems</th>
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<td>Percutaneous catheter</td>
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<td>Percutaneous catheter with subcutaneous tunneling</td>
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<td>Implanted catheter with subcutaneous injection site</td>
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<td>Implanted catheter with implanted reservoir and manual pump</td>
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<td>Implanted catheter with implanted infusion pump</td>
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There are five types of neuraxial drug delivery systems (Table 1).[3] Prior to understanding the criteria for selecting the appropriate drug delivery system and its respective advantages and disadvantages, it is necessary to become familiar with the technology of each system.

**Percutaneous Catheter (Type 1)**

In essence, percutaneous catheters are identical to the catheter systems used for continuous epidural anesthesia or continuous subarachnoid anesthesia during surgery and postoperative epidural analgesia. By definition, these catheters are designed for short-term use. They are made of nylon, polyurethane, or polyamide and can cause localized tissue reactions at the site of insertion.[4] As in their use for postoperative analgesia, these catheters may potentially migrate into the subarachnoid or intravascular space (if placed epidurally).[5] Extrapolating from the large postoperative experience, the incidence for both types of migration is about 0.2%.[5] Because these catheters are not designed for long-term use, mechanical problems appear over time: premature dislodgement from the epidural or subarachnoid space, catheter obstruction or kinking, and failure of the catheter adaptor/connector. All these factors combine to make this system suboptimal for truly protracted use.

**Percutaneous Catheter With Subcutaneous Tunneling (Type 2)**

Percutaneous catheters may be tunneled underneath the skin.[6] Once again, the catheters used in this system are identical to those used for both intraoperative anesthesia and postoperative analgesia. It is assumed that tunneling reduces the incidence of dislodgement from the intended space for drug delivery.

**Implanted Catheter With Subcutaneous Injection Site (Type 3)**
The implantation of this type of delivery system (and the more technologically advanced neuraxial drug delivery systems) requires a minor surgical procedure and should therefore be performed only in a sterile environment. Fluoroscopy is essential for verifying proper placement of the catheter tip. Irrespective of intended epidural or subarachnoid placement, the needle is best inserted using a paramedian approach. Such an approach obviates the sharp angulation created by the midline approach.

Using local infiltration analgesia, a paravertebral incision is then made around the needle entrance site with the needle in place to avoid laceration of the catheter. A catheter exit site or port site is then chosen, and appropriate tunneling of the catheter(s) is performed.

Theoretically, epidural catheter insertion may be as high as the end of the epidural space at the level of the foramen magnum. Subarachnoid catheters are easier to thread over long distances and have even been placed intracisternally.[7] At minimum, both epidural and subarachnoid catheters should be advanced at least two vertebral levels above the point of insertion, thereby allowing for inadvertent withdrawal of the catheter during the remainder of the procedure. Fluoroscopy with contrast injection is used to verify proper epidural or subarachnoid placement.

There are two design types for implanted catheters with subcutaneous injection sites: 1) implanted but exteriorized catheters (in contradistinction to merely tunneled catheters) and 2) subcutaneous ports with completely internalized catheters.

The DuPen silicone-rubber catheter (CR Bard, Inc., Salt Lake City, UT) is of the implanted exteriorized type (Figure 2). This is a dual catheter system with insertion of a distal, smaller diameter catheter into the epidural space, tunneling of a larger proximal catheter from the exit site to the back, and connection of the catheters. The proximal catheter is exteriorized and connected to an adaptor for injection or continuous infusion.

The catheter design is notable for the presence of a Dacron cuff positioned approximately 5 cm internal to the catheter exit site. Epithelization of the cuff theoretically reduces the risk of catheter dislodgment. Patient-controlled analgesia is achieved by connection to an external, appropriately programmed infusion device.

The second type of implanted catheter system with a subcutaneous injection site is a portal system (eg, Port-a-Cath, Pharmacia-Deltec, Inc., St. Paul, MN) (Figure 3). [9] This is a totally internalized system. The stainless steel port contains a 60-m screen filter that is connected to the catheter. The catheter is inserted in the epidural space, using essentially the same technique as described previously. The catheter is tunneled from the back to the site for the port pocket. The port pocket is created in subcutaneous tissue in an area that is supported by bone, usually a rib, so as to facilitate needle insertion. The rib gives firm support to the port (ie, a “back-stop” mechanism). The pocket is created with a 1-cm layer of subcutaneous fat above the port and the port is then sutured to the fascia to prevent inversion.

To administer medication, the port must be accessed. A noncoring needle must be used to allow repeated access to the port and prevent damage to the septum. Patient-controlled analgesia or continuous infusions are possible by continuous access and connection to an external, appropriately programmed infusion device.

**Totally Implanted Catheter With Implanted Reservoir and Manual Pump (Type 4)**

**FIGURE 4**

The AlgoMed System

The AlgoMed implantable patient-activated device (Medtronic, Inc., Minneapolis, MN; in development and not yet commercially available in the United States) (Figure 4) is composed of an implanted reservoir with a manual pump.[10] The design is novel because it is specifically a demand-activated system. Thus, by definition, analgesia is patient-controlled. Continuous infusions are not possible. The silicone infusion device is composed of a subarachnoid catheter, a drug reservoir, and a control
pad. The infusion control pad is implanted over the lower thoracic area with the reservoir in the adjacent upper abdominal area, usually around the belt line. In order to receive a dose of medication (1 mL) in the subarachnoid space, the patient must simultaneously depress the activation valve and the pumping chamber. The patient cannot then reactivate the device until the pumping chamber has refilled in 1-hour’s time (ie, a “lockout interval”). Dosage is limited by a volume of 1 mL per demand and may be varied only by changing the concentration of drug within the reservoir (similar to the Infusaid Model 400 and Arrow M-3000 infusion pumps). When appropriate, the reservoir is refilled by inserting a needle into a subcutaneous port in the control pad. At present, there has been too little experience with this particular system to comment upon any of its advantages, disadvantages, or technologic problems.

Totally Implanted Catheter With Implanted Infusion Pump (Type 5)

The first commercially available implanted infusion pump in the United States was the Infusaid Model 400 (Infusaid Corp., Norwood, MA).[11,12] The drug delivery system worked via a propellant gas placing pressure around a drug chamber contained within a bellows system. A single slit aperture leading to a catheter made the pump suitable only for continuous infusion. The rate of infusion was immutable and set at the factory. The only possible way of changing the amount of drug the patient would receive was by changing the concentration of the drug in the chamber. A side port allowed bolus injections, but the design of the side port was problematic. Inserting the needle incorrectly within the side port during pump refill could result in overdose. The Infusaid pump is no longer available, and has been superseded by the Arrow M-3000 (Arrow International, Walpole, MA)—also a totally implanted continuous infusion device (Figure 5). The pumping mechanism for the Arrow M-3000 follows the same design as that of the Infusaid device with a preset flow rate. Dosage can only be changed by alternating drug concentration within the pump. Pump volume is 30 mL. Unlike its predecessor, however, the pump contains only a single raised septum without a side port. Percutaneous bolus injections may be administered by use of a special noncoring needle with a needle shaft aperture and closed needle tip that directs fluid away from the drug reservoir chamber and directly into the catheter. Theoretically, such a design is advantageous as it obviates the need to search for a side port. Reliance upon proper type of needle insertion for refill or bolus rather than correct septum insertion eliminates the potential for overdose. FIGURE 6

The Medtronic SynchroMed Programmable Implantable Infusion Pump

The Medtronic SynchroMed Programmable Implantable Pump (Medtronic Neurologic, Inc., Minneapolis, MN) (Figure 6), in essence, uses cardiac pacemaker technology to generate programmability. The SynchroMed pump mechanism consists of a lithium battery-driven peristaltic infusion pump with a collapsible drug reservoir, and an electronic module with microprocessor-based circuitry and an antenna. An external programmer head communicates with the antenna using radiofrequency signals, much as in cardiac pacemakers. A propellant gas once again surrounds a bellows system containing the drug reservoir. The programmer may be used to change the function of the peristaltic pump thus allowing the device to be programmed to give single injections, continuous infusions, multiple boluses, or complex continuous infusions. The pump has a central reservoir and an access (side) port. Reservoir volume is 18 mL. The side port is used only occasionally for bolus injections because they can be programmed; it is most useful for injection of contrast to check for catheter patency. A 22-gauge noncoring needle is used to access the central reservoir for drug refill. A 25-gauge mesh overlies the side port preventing overdose by inadvertent needle insertion during pump refill. A 25-gauge noncoring needle must be used specifically to access the side port for bolus administration. The SynchroMed infusion system is a commercially successful design, in widespread use.[13,14]
Appropriate System Selection for the Individual Patient

The selection of the appropriate neuraxial drug delivery system for an individual patient is based upon several considerations: 1) patient life expectancy, and its corollary; 2) cost effectiveness in light of limited life expectancy; 3) choice of epidural vs subarachnoid route of administration; 4) risk of infection; 5) location of patient (for refills and troubleshooting); 6) dynamics of the pain condition (frequent dosing and medication changes favor epidural systems); and 7) need for frequent patient-controlled bolusing. On the other hand, appropriate catheter location does not mandate the use of a particular neuraxial drug delivery system.

Catheter Location

Catheters may be placed regionally along the neuraxis for intracisternal, [8] cervical,[8,15,16] thoracic,[17] and lumbar administration of agents. However, where a catheter tip is placed is mandated by 1) the location of the pain, 2) the type of pain (neuropathic vs somatic or visceral), and 3) the choice of analgesic. The use of local anesthetics for the treatment of neuropathic pain will require that catheters be positioned along the neuraxis in proximity to the nerve root appropriate for the dermatomal distribution of the pain.[18] Visceral and somatic pain are more easily treated with opioids. For hydrophilic agents, there may not be any advantage to placing a catheter tip at a more rostral location such as the midthoracic and cervical cord.[19] Low thoracic or lumbar administration of hydrophilic agents may be adequate for the purpose.

Life Expectancy and Cost Effectiveness

It has long been an axiom that increased life expectancy mandates the choice of a neuraxial drug delivery system with increased technologic sophistication. This usually signified the use of pump systems for patients with protracted life expectancies. Given the difficulties in estimating length of survival, [20] choosing the most appropriate neuraxial drug delivery system (except in the most obvious of cases) may be challenging. However, some evidence exists that after 3 months, implanted pump systems may be a more viable financial alternative than totally implanted catheters with subcutaneous injection sites.[21] Unfortunately, this study by Bedder et al.[21] was not randomized, blinded, or controlled. The financial ramifications for choices among other neuraxial drug delivery systems (eg, DuPen catheter vs Port-a-Cath) are even more obscure.

In general, it is assumed that percutaneous catheters or percutaneous tunneled catheters are best suited for patients with very limited life expectancies (< 1 mo) because of the potential for dislodgement and the theoretically higher risk of infection. Although initial expenditure for implantation of an infusion pump system can be large, less technologically sophisticated systems may become more expensive if survival is prolonged, due to the cost of home care and maintenance.[21,22] Pharmacoeconomic modeling of the criteria for choice of individual neuraxial drug delivery systems remains an important topic for future research.

Epidural vs Subarachnoid Drug Delivery

The epidural and subarachnoid routes of administration can be equally effective in managing intractable cancer pain.[23,24] Once again, expected duration of therapy appears to guide choice of method of drug administration. Catheter obstruction, fibrosis, and loss of analgesic efficacy are well described in the literature for epidural drug administration over time.[25-29] Thus, subarachnoid administration would seem most appropriate for protracted duration of therapy.

With the increased potency of subarachnoid drug delivery[30] and decreased dosage requirements, a decreased incidence of side effects would be theoretically expected. Moreover, subarachnoid drug delivery may be used effectively in the presence of extensive epidural metastases.[31] Extensive epidural metastases could potentially impede access of epidurally administrated medications to the areas of the spinal cord most appropriate for analgesia.

Of note, subarachnoid granulomas are now being described in patients with chronic subarachnoid catheterization, highlighting the need for heightened awareness of new neurologic findings in patients with these systems.[32] However, despite the accumulating evidence that granulomas may occur with protracted subarachnoid drug delivery, subarachnoid delivery remains the preferred method of drug administration if the patient’s life expectancy is estimated to be greater than 3 to 6 months.

Infection Risk
Infections of neuraxial drug delivery systems may be classified as 1) superficial (skin) infections, 2) port or pump pocket infections, 3) deep track infections (cellulitis), and 4) epidural abscess or meningitis.[33] The most common pathogens responsible for these infections are gram-positive skin flora, most notably Staphylococcus aureus and Staphylococcus epidermidis.[33-35] Gram-negative pathogens may also be found but with a lower incidence.[33] Potential mechanisms of infection include 1) poor surgical technique, 2) bacterial contamination of exteriorized catheters with extension along the catheter track to deeper tissues, 3) administration of contaminated injectate, 4) direct extension or hematogenous spread of infection from another site, and 5) poor patient hygiene. It has been assumed that a linear relationship exists between the duration of implant of an exteriorized catheter and the rate of infection: the longer the catheter remains implanted, the higher the risk of infection. While this may seem intuitive, no study directly compares the rate of infection among various neuraxial drug delivery systems. Two studies describe an infection rate (excluding superficial infection) per day of use for an exteriorized epidural system (1 per 1,702 days of catheter use)[33] and an exteriorized subarachnoid drug delivery system (1 per 7,242 days of catheter use).[36] Despite these two studies, it would seem axiomatic that the older the exteriorized catheter system, the higher the probability of an eventual infection.

Portal systems have been advocated as having less risk of infection than exteriorized catheter systems. Portal systems offer the advantage of being totally implanted. Because they do not require any external care when not in use, portal systems theoretically represent a decreased risk of epidural or subarachnoid space or track infection. With the need for access (ie, repetitive bolus injections or continuous infusion) the advantages of a port may be lost.[36,37] It would also seem intuitive that the cerebrospinal fluid would represent an excellent “culture medium.” Thus, any exteriorized catheter intended for protracted use should not be placed directly into the subarachnoid space. Chronic epidural space catheterization would seem to have less infectious risk. A raging debate now exists over the advisability of protracted delivery of drug to the subarachnoid space via exteriorized systems because of growing experience with such systems.[4,36,38-40] Once again, it would seem obvious that a higher risk of infection exists for exteriorized subarachnoid catheters, with longer use.

**Conclusion**

**TABLE 2**

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<tr>
<th>System</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
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<td>Type 1</td>
<td>Simple to use</td>
<td>More involved surgery for placement</td>
</tr>
<tr>
<td>Type 2</td>
<td>Simple to use</td>
<td>More involved surgery for placement</td>
</tr>
<tr>
<td>Type 3</td>
<td>Simple to use</td>
<td>More involved surgery for placement</td>
</tr>
<tr>
<td>Type 4</td>
<td>Subcutaneous delivery</td>
<td>More involved surgery for placement</td>
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There are many and varied technologic choices for neuraxial drug delivery for intractable cancer pain. Ultimately, selection of the appropriate system for the individual patient will be based upon 1) life expectancy, 2) cost considerations, 3) choice of epidural vs subarachnoid drug delivery, and 4) acceptance of a particular “level” of infection risk. The advantages and disadvantages of each neuraxial drug delivery system are reviewed in Table 2.

Quite often, the choice of appropriate delivery system is not as “clear cut” as it would seem, particularly for patients with a life expectancy of 3 to 6 months. Development of econometric models for selection of appropriate neuraxial drug delivery system(s) within the confines of particular clinical scenarios would represent a major clinical advance.

**References:**


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