Complications of Neuraxial Infusion in Cancer Patients

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Intraspinal drug delivery systems can be effective in controlling intractable pain. However, before these invasive pain therapies are initiated and to avoid or minimize any complications associated with their use, there

Introduction

The use of intraspinal drug delivery systems in a comprehensive, palliative care treatment plan can be an effective means of controlling intractable pain states.[1-4] The decision to move to an invasive therapy should be based on a thorough understanding of the etiology of the pain and related pain generators, the underlying cancer, and antineoplastic therapy. The topic of complications of neuraxial infusion devices must include these factors and address device selection as it relates to the avoidance of potential risks. For example, the assumption by some anesthesiologists that intraspinal cannulation is contraindicated in all patients with known vertebral metastatic lesions is not supported in clinical practice. A majority of spinal metastatic lesions involve the vertebral body, which is distant from the dorsal position of the intraspinal catheter.

Perceived and True Complications

In one review of 200 patients with spinal metastatic disease, only seven had disease that obliterated the canal, whereas 26 had some partial obstruction of the space.[5] A strong suspicion of myelopathy or cauda equina syndrome should prompt MRI review, radiation oncology or surgical consultation, and a reappraisal of the likelihood of success with neuraxial analgesia. Other assumed contraindications to neuraxial infusion techniques include history of septicemia, chemotherapy-related leukopenia, risk of thrombocytopenia, etc. It is clear that patients with cancer-related pain will undergo chemotherapy and will have times when their immune systems are compromised by therapy. This will result in a lowering of platelet counts, leukopenia, and possible septicemic episodes. Will these episodes result in a direct risk of complications related to the neuraxial infusions and be a contraindication to those infusions? Is there a specific level of thrombocytopenia at which implantation is contraindicated? Is the presence of active septicemia a true contraindication, whereas a history of septicemia only a risk factor? All of these issues require clarification.

The one area in which contraindication to implantation appears clear is with thrombocytopenia. Cancer patients with low platelet counts and/or anticoagulation therapy are commonly encountered. Our policy in pain management, developed in close collaboration with medical oncology, is to proceed if the platelet count is at least 20,000 without any signs of subcutaneous ecchymosis. Platelet transfusion decisions are made jointly by the pain specialist and the hematology-oncology specialist. Reversal of anticoagulation therapy is decided on a case-by-case basis with consultation from the oncologist.

Based on extensive experience, the only pragmatic contraindications to neuraxial infusion device implantation are those also relevant to surgical intervention. Psychosocial contraindications, of course, should also be considered preoperatively.

Side Effects

A prerequisite to a discussion of complications is a review of side effects. The side effects of drugs used in implantable devices, including both externalized devices and implantable pumps and ports, should be considered before implantation. A careful review of the patient[s]'s past drug history is critical. The clinician should determine if the patient can tolerate the drugs available for infusion to achieve functional analgesia. Patients who are intolerant of opioids and are implanted may well suffer from side effects that preclude the successful use of the implanted device for infusion of those opioids. Although it is true that much lower doses of opioids will be required via a neuraxial route, careful screening is warranted. In addition, the clinician should consider the use of synergistic drugs
for infusion to lower the overall dose requirements and hopefully to avoid the side effects seen with a single-drug infusion. Some examples of drug synergy seen during intrathecal or epidural infusion are opioid-clonidine; opioid, clonidine, and local anesthetic; or clonidine-local anesthetic. When clonidine is added to the infusion, the opioid and local anesthetic agent should be decreased by 30%. A complete understanding of the potential complications and side effects associated with implantation, drug infusion, and long-term device care and maintenance is essential before entering into a contract for patient care. Cancer-related pain management requires a constantly evolving care plan responsive to pain and tumor progression, and a vigilant awareness of potential complications and side effects. The care plan should ensure that new pain symptoms are diagnosed and treated, complications are identified and corrected, side effects of analgesics are identified and treated, or sequential drug trials are initiated.

Complications related to implantable devices fall into several categories.[6] Infection is the most feared complication. Although the risk is real, often the fear alone leads to implantation delays or to discounting implantation as a clinical option. Complications discussed in this article include infection, drug-related complications, device failure, and complications associated with the use of individual devices.

**Infection**

Infection is arguably the most significant risk in the mind of the practitioner when the decision is made to proceed with implantation of an infusion device. The data on the risks of infection after implantation of either an externalized or buried device are unclear. There is a lack of prospective epidemiological studies of infection associated with device implantation. We are, therefore, limited primarily to a discussion of the causes of device-related infection based on individual experience without the benefit of those studies.

The sources of contamination include direct contamination during implantation, hematogenous spread during septicemic episodes, a track infection in externalized devices, contamination during access of an implanted device, and contamination of the infusion drug.[7] Sterile conditions must be maintained during all operative and access procedures.

Externalized devices are considered to have the greatest risk of contamination. The contamination of these devices is generally considered to occur along the path of the catheter from a skin source. Our experience with the long-term epidural catheter indicates a 5% to 15% infection rate.[7,8] Infections related to implanted intrathecal access devices are rare and even more rarely reported.[9-11] These and other reports in the literature are by individual practitioners, and lack the strength of a prospective epidemiological study design.

**Externalized Catheter Infections**

Externalized catheters used to gain access to the intrathecal and epidural space have been in general use around the world. Most recently, the use of externalized intrathecal catheters for long-term infusions has been reported from Sweden.[12-14] In some cases, the devices have been used for prolonged infusions with low rates of infection (0.5%).[14] It is interesting to note that the technique used for infusion included monthly tubing and filter changes. This is markedly different from the standard in the United States, which involves changing the pump tubing and filters every 24 to 72 hours.

The reported results suggest that the policies now in effect in most US hospitals, which are based on infections related to IV infusions, deserve a new evaluation. Some report the frequency of infection in externalized catheters is based on the number of days of implantation, thus trying to reflect the risk of long-term implantation. If the duration of implantation has a significant role in the frequency of epidural infections, then all the factors that are affected by duration of use should be examined. A close examination of epidural catheter-related infections should include an examination of the risk factors and the specific site of infection. Presumed risk factors include general body hygiene, septicemic episodes, and presence of a colostomy, ileostomy, or other infection source (eg, an abscess).

Catheter-related or device-related infections are documented as such, but rarely is the specific site or extent of infection discussed. To understand the cause of infection, we must first know what tissues are involved and how the infection progressed to the point of diagnosis. This can only be determined by obtaining cultures of the suspected sites of infection. Cultures of the withdrawn catheter will sample the whole length of the catheter track, without separating the epidural space from the catheter exit site. The procedure for an epidural aspirate culture is outlined in Table 1. The following series of cultures will allow the clinician to diagnose the organism involved in the infections.
and the source of infection:

1. Aspiration culture of the epidural space through the catheter
2. Aspiration (needle) culture of inflamed track infection (avoid catheter puncture)
3. Culture of the catheter exit site
4. Culture from distant sites of known infections
5. Culture of other possible areas of contamination
   - Sputum
   - Urine
   - Colostomy or other ostomies
   - Nasal

The culture results may indicate a specific result:

- A positive culture of the epidural space with a negative culture from the catheter exit site indicates the epidural space was contaminated through the infusion and not along the catheter track.

- A positive culture of the epidural space with the same organism identified from the exit site might indicate the source is either the skin organism contamination of the infusion or a tracking of the infection along the catheter track. Physical examination should help in this determination.

- A negative culture from the epidural space, but a positive culture from the catheter exit site and clinical findings of inflammation along the catheter track, are consistent with an extension of the catheter track infection, but with presumed preservation of sterility of the epidural space. Aggressive care is mandatory to prevent extension.

- All cultures are compared to determine the relationship between the suspected area of infection and possible sources.

The standard treatment of epidural catheter-related infections involves identification of the organism, followed by device removal, and aggressive antibiotic therapy. After treatment, the patient can have the device replaced for continued pain management, if desired. However, this author [8] and others [15] have successfully treated indwelling epidural catheter infections with epidurally administered vancomycin (Vancocin) in the very rare patient for whom catheter salvage is the paramount concern.

The use of inline catheter filters during long-term use is generally accepted. The use of a double-filter technique has resulted in a marked decrease in catheter-related infections.[8] The proximal filter is never changed unless damaged. The outer or distal filter and pump tubing are changed on a monthly basis. The author has experienced only two catheter-related infections in 75 patients (3%) in the past 2 years with this technique.

**Port- and Pump-related Infections**

Infection related to ports and pumps may be seeded from a distant source, from a contaminated injectate, or from a breakdown of the skin barrier by wound dehiscence or local skin infection.[16] In the author’s experience, postoperative infections are the most common source of early infection in these devices. Infections are rare in pumps during treatment, but theoretically may occur more often in ports, which are usually accessed more often, or have continuous access and may then approach the same risks seen with externalized catheters.

Noncoring needles are used for access of both ports and pumps. Most pump manufacturers have
special needles to access their systems. The needle size and design are specific for the reservoir port and avoid the possibility of depositing the drug directly into the intrathecal space. Sterile conditions during the access must be maintained. Infected or inflamed tissue should not be entered during the refilling of an implanted device.  

The identification of infections related to these devices requires a high level of suspicion based on clinical history and examination. The specific organism must be identified and its potential sources isolated before treatment. Where warranted by clinical examination, a skin culture and aspiration culture from the device pocket may be necessary. An aspiration culture should not be obtained from the device itself until the status of the pocket is first determined. This will avoid the risk of contaminating a very expensive device, which may be potentially saved by treating an isolated pocket infection.  

If a gram stain of the pocket is negative, but there is still a suspicion of an infection within the device or the neuraxial space, then an aspiration of the inside of the port or pump needs to be taken. These gram stains and cultures should be obtained before antibiotic therapy is started to ensure identification of the organism. In emergent clinical situations, eg, when signs of meningitis are present, there may be no time for formal culture results. A gram stain of the pump/port pocket will suffice in making a decision about when to go ahead with a device aspiration culture. If fluid aspirated from the pump or port results in a positive culture, the device should be removed. Early *Staphylococcus aureus* or *epidermidis* infections of the device pocket may be treated with IV vancomycin, but infection from gram-negative, yeast, or acid-fast organisms will require device removal. It is important to identify the offending organism and to determine the extent of infection before establishing a treatment plan. Those practitioners who have less experience in treating device-related infections should obtain an early consultation from an infectious disease specialist.  

### Drug-Related Complications  

Drug-related side effects are the most common adverse event experienced during neuraxial analgesia. Side effects include but are not limited to nausea, vomiting, sedation, delirium, myoclonic jerking, constipation, and hypotension (Table 2). These side effects, if undetected and untreated, may result in termination of the neuraxial infusion. Minor side effects can be treated. Major side effects may require sequential opioid trials or alternative drug therapy [clonidine (Duraclon) or local anesthetic agents] to relieve symptoms.  

Drug errors may occur at any time, in any pharmacy, and at any point from the pharmacy to the patient’s pump. The drug errors fall into one of several categories described in Table 3. When an unexpected clinical finding is identified, the drug infusion or content of the device should be checked against the order. When an implanted device is in use, the unexpected clinical picture may reflect an error in the drug concentration issue. When the actual drug content cannot be determined, but the index of suspicion for drug error is high, the device should be refilled with a newly mixed solution. When there is suspected patient injury, the contents of the device should be sent to an independent laboratory for analysis, both qualitative and quantitative. This is not a medicolegal analysis, but an effort to identify the offending agent so specific treatment may be started.  

Drug errors usually do not result in any permanent patient injury. Correction of the error is usually the only required action. There is, however, the potential that a drug error could cause a permanent injury including paralysis. Some examples include use of drug preparation containing preservative for long-term intrathecal infusion (Demerol, morphine with phenolformaldehyde). If there are definitive data to prove a drug error, such data should be disclosed and discussed with the patient. There are unpublished reports of the total refill dose of opioid being infused directly into the intrathecal space. Such a massive overdose could, if not detected during injection, lead to death or permanent neurologic injury. One pump manufacturer, Medtronic, has designed a screen that fits over the side port of the SynchroMed pump to allow only 25-gauge needles to enter the side port; using the specialized 22-gauge noncoring refill needles for refilling the reservoir port of this pump will avoid this risk. Another manufacturer, Arrow, has a special needle and injection port that avoids this risk if used as directed.  

If a drug error of any kind is noted, immediate action is necessary. The patient (if not at the physician’s office) should be called to return to the office or to present to an emergency department. The drug used to fill the device should be removed, and if necessary the device should be flushed with normal saline. The correct drug and concentration should be used to fill the device for infusion. Drug errors found during epidural or intrathecal externalized infusions should be
handled in a similar manner.

**Device Failure**

The question of device failure should be considered (after drug errors) when an unexpected clinical picture is seen in a patient who has been stable with no clinical reason for the change. Hospital admission may be required to obtain stabilization as diagnostic studies are obtained. The integrity and functionality of the implantable device should be determined, either by radiological or aspiration studies.

**Catheters**

Externalized catheters or those connected to ports or pumps may have the following causes of failure to function:

- Not in expected location
  - a. Implantation error
  - b. Migration of catheter:
    - Intrathecal to epidural
    - Subcutaneous
    - Along nerve root

- Restriction of flow
  - a. Tubing kink
  - b. Mechanical obstruction
  - c. Fibrosis

Catheters either in the epidural or intrathecal space may be analyzed for position with a simple lumbar spine film. The absence of a visible neuraxial catheter on film should be compared to the postoperative films, whenever possible. The author has noted that there may be production errors, for example, failure to include barium in a particular shipment of catheters. A simple injection of water-soluble dye through the catheter will confirm catheter presence and position. A postimplantation spine film or epidurogram establishes the original catheter position for future reference.

Implanted port and pump catheters may be analyzed with a side-port injection using water-soluble dye under fluoroscopy. Intrathecal pumps, ports, and catheters may be aspirated; if a free flow of cerebral spinal fluid is identified then the intrathecal catheter position is confirmed. Pumps without side ports do not allow this type of analysis and may require a computed tomography myelogram to identify catheter position.

The clinician should be aware of the dead space of the pump, port, or catheter in determining the volume of dye required to fill the catheter. If the dye is injected, before aspiration of the catheter, the patient will receive a significant dose of drug (displaced from the catheter). In the case of an epidural catheter, the volumes of infusion are usually large, compared to the dead space, and the dose lost or given during the dye study is insignificant. But, in the case of an intrathecal pump, this volume may be very significant.

The catheter space occupied by the dye or cerebral spinal fluid should be considered when the pump is restarted, or when the first dose of epidural or intrathecal drug is administered. The average pump catheter has a ± 0.4 mL volume, which may be up to a 4-day dosage if the pump is administering only 0.1 mL per day. In the case of an opioids only infusate in a patient tolerant to opioids, this will not likely be a catastrophic overdose event. However, if it takes 4 days for the patient to again receive the opioid infusion, the patient could have significant opioid withdrawal. In the case of intrathecal clonidine, a several-day acute withdrawal from a high dose of clonidine may result in rebound hypertension.

Pump problems may be an issue of battery failure or pump mechanism malfunction. Battery failure is usually predictable and the pump will give warning of pending battery failure at the time of pump refill, or it will release an alarm if the failure was not detected early enough. In the case of a pump mechanical malfunction, there is no warning although this is an extremely rare occurrence. However,
if the patient has an acute loss of analgesia, with no discernible reason, the contents of the pump should be checked to see if the residual volume in the pump is excessive. If so, the practitioner should suspect pump failure. Most pumps function with a < 10% error. One may rarely identify a pump with a 15% to 20% variance (faster or slower); in these cases, the pump should be replaced. The manufacturer of the pump should be contacted for their input before its replacement. If acute pump failure occurs, the manufacturer has a diagnostic protocol to follow to determine if the ports are plugged or if the pumping mechanism has failed or is temporarily not functioning.

Complications Associated With Individual Devices

All devices manufactured and sold in the United States require approval from the FDA section on devices. This may be a simple process that gives the manufacturer permission to enter into the market with an approved device that complies with the same manufacturing requirements as other companies producing a similar product. There are some products sold in the United States that do not have, and have never applied for, this certification. Most national and international professional organizations restrict products to be displayed during meetings to approved devices. Although the oversight committees do not investigate all products on display, for the most part, products displayed at these meetings have FDA approval for sale.

Externalized Catheters

Externalized catheters may be used to gain access to both the epidural and intrathecal spaces for neuraxial analgesia. Most of the United States literature deals with epidural infusions, but recent articles from Europe discuss the use of externalized intrathecal catheters.[2-4] There are advantages and disadvantages to both procedures, but the complications seen with the two procedures are as vastly different as the infusion drug concentrations and infusion rates. Therefore, to discuss complications and their clinical signs we first need to understand the use of the two techniques, the pharmacodynamics, and the clinical titration of the infusions.

Epidural catheterization for the control of cancer-related pain could easily be achieved using both temporary and permanent catheters. The choice of catheter type is a clinical decision based on the expected duration of infusion and catheter tip position. Temporary catheters are made from polyurethane, polyamide, and nylon. The main procedural issue with the temporary catheter materials is the softness, flexibility, and relative stiffness during insertion. The stiffer the catheter and stylet the greater the chance of dural puncture. Very soft catheters are difficult to control if catheter tip position is important. Both catheter types are radiopaque, but very small and difficult to visualize on lumbar spine films without radiopaque dye. Therefore, if catheter malposition is being assessed, temporary catheters will require an epidurogram to determine their position.

Hardware problems with temporary catheters include kinking, curling, catheter breakage, catheter withdrawal, and luer-lock adapters falling off. Drug-related problems are usually related to the infusion and the drug combination used for the infusion.

Intrathecal externalized catheters are used for cancer pain management in Europe.[18-20] General use of this technique has not gained wider clinical support due to the fear of infection leading to meningitis. As seen with epidural catheterization, there are no aggregate studies outlining the risk of infection in cancer patients. It would seem that with meningitis as the presumed adverse outcome, clear patient selection criteria for externalized intrathecal access would be imperative. Intrathecal catheterization may be necessary in patients with intractable pain, for whom access to the epidural space is limited by tumor, radiation fibrosis with obliteration of the epidural space, or other mechanical obstructions that prevent the flow of drug.

Pumps

Neuraxial pumps are available with two general infusion systems; each of these has a unique history of complications. The first is the computer controlled, battery-powered Medtronic SynchroMed pump, which has an 18-mL reservoir volume and an adjustable infusion volume. The second is the constant infusion fixed-rate pump powered by Freon gas, now produced by Arrow. Each of these neuraxial pumps has a different set of potential complications and treatment plans.

Medtronic SynchroMed Pump Problems that disrupt the normal function of the SynchroMed pump may include operator error; battery failure; pump mechanism malfunction; diaphragm leakage; and computer failure.

Drug-related errors are generally the result of operator error. It is a good policy to always have two people check the initial programming and subsequent programming changes. Programming errors that can occur include substituting micrograms for milligrams or milliliters. Such an error has the potential of causing a 10-fold increase or decrease in expected dose delivery. Programming errors
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are usually detected by a marked increase in pain symptoms or sedation and an early pump alarm. A computer analysis of the program and the alarm status of the pump would easily identify these errors. In most specialists’ offices, an internal double-check system should avoid such errors, but these errors may occur even in the best of hands. It is important that the patient and the patient’s family have emergency access to the pump providers.

Accidental side-port access is another potential hazard. The pumps have both a reservoir port and a side port. The side port is used to access the intrathecal space to clear the catheter when a drug or concentration is being changed, to sample the intrathecal space, and for contrast injections to determine catheter position. Using a different-sized needle to access the side port virtually eliminates this error.

Device failure can occur for a number of reasons. Battery failure is a potential problem that is usually detected early by a computer warning. Theoretically, a patient with a hearing loss may not be able to hear the low battery alarm and this could lead to battery failure before the warning is detected. Pump failure is most significant for drug withdrawal symptoms. These symptoms vary in severity and risk depending on the medication and dose infused. Baclofen (Lioresal) withdrawal may result in increased spasticity, opioid withdrawal can result in classic signs of abstinence, and clonidine withdrawal could result in rebound hypertension. The hypertension of acute clonidine withdrawal carries the potential for a cerebrovascular accident in patients with predisposing factors.

Failure of the actual pump mechanism itself is rare but may occur and can be detected by an acute loss of analgesia with an unexpectedly high level of drug in the reservoir. The position of the pump can be evaluated by radiography before and after a bolus is programmed, to determine if the armature of the pump is rotating. Reprogramming and restarting the pump may reactivate the failed device. In some cases, the pump will have to be replaced.

Patients who opt to terminate their therapy should contact their providers for advice to avoid withdrawal and to avoid damage to the implantable device from nonuse. Externalized devices should either be removed or their patency maintained with irrigation every other week. A time for device removal should be established. Implantable pumps should be drained, filled with normal saline, and turned off.

Programmable pumps allowed to remain empty without being turned off and filled with saline may result in early battery failure and/or precipitation of the drug contained within the pump. Constant flow pumps should be refilled with saline on a periodic basis. Implantable pumps should not be abandoned without medical follow-up care. When patients transfer their care, records of infusion and treatment plans should be forwarded to the new clinician. Families of patients who are planning cremation following death should be made aware of the risk of explosion of the implanted device during cremation.

**Constant Infusion Pumps**

The fixed-rate pumps have been available for a longer period of time than have the programmable pumps, and there have been several manufacturers. Complications associated with fixed-rate pumps are equivocal, but the techniques for handling the problems are unique to each pump.

The Arrow pumps have a distinct access needle that allows aspiration of the side port while avoiding the risk of instilling the reservoir volume. This class of pumps has no battery or computer program to address. The primary complications are related to drug preparation and pump filling. The second area of risk is in the pump diaphragm. Drug may leak out of a faulty diaphragm into the pump pocket. Particulate matter may obstruct the ports of the pump and cause a potential complication. Failure of pump function (not due to catheter failure) is usually related to obstruction of flow or diaphragm leakage. These can be detected by checking on the residual volume left in the pump.

**Ports**

Ports are available for access to both the epidural and intrathecal spaces, but the FDA has not approved any ports specifically for intrathecal infusions. There may be a different rate of hardware failure depending on the specific manufacturer. Ports may leak from connections or diaphragms may become disconnected or infected. Intrathecal ports have the risk of spread of a port pocket infection along the track, resulting in meningitis intrathecally.

Determining the specific failure should be relatively simple. The catheter failure analysis is outlined above and should be checked first. The port pocket may be aspirated for culture. A dye study is generally used to determine if there is a leak of the port diaphragm or connections.

**Psychosocial Issues**

Complications related to implantable devices must include a discussion of the psychological impact of implantation. In cancer pain management, when the pain is due to the tumor or treatment of the
tumor, the patient relates the pain to the tumor diagnosis. Many device manufacturers, third-party payers, and clinicians recommend that a psychological or psychiatric consultation be obtained before device implantation. Patients are dealing with the pain, the potential of impending death, and body image implications of implantation. It is easy to understand why there are situations where the issues surrounding implantation become greater than the issues of pain relief. The psychosocial assessment of an individual experiencing cancer-related pain is complex and not always easy to determine. A psychological consultation may raise issues that need to be explored further prior to an implant.

**Summary**

Most device-related complications cannot be completely avoided, even in the best medical practices. Careful patient selection may contribute to avoidance of some complications. Constant vigilance is the best defense against errors. Early detection of errors in drug delivery and early detection and aggressive management of infection are critical areas of competency for providers of neuraxial pain management.

**References:**


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