Hepatic Artery Infusion Pump in the Treatment of Liver Metastases

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Background: Hepatic artery infusion pump (HAIP) use in chemotherapy started in the 1960s as a way to treat liver metastases that were not amendable to locoregional therapy or surgical resection. Because of complications and limited survival benefit, the use of HAIPs fell out of favor. A resurgence has occurred in the use of these pumps, but limited information is available in the literature guiding nursing care of these patients.

Objectives: The purpose of this study was to review the literature regarding the use, procedures, and nursing care of patients with HAIPs.

Methods: A systematic literature review was conducted to obtain a comprehensive range of publications.

Findings: Database searching resulted in 511 titles and abstracts. After eliminating duplicates and nonrelevant titles, 65 remained and were read in full. Of these, 20 were excluded because they did not fit the inclusion criteria.

Liver metastasis is commonly the first site of distant metastases from cancers of the breast, gastrointestinal tract, uveal melanoma, and hepatobiliary system because of the liver’s large blood supply (Barber & Fabugais-Nazario, 2003; Nishiofuku et al., 2010). Patients with a limited number of liver metastases may benefit from improved survival from surgery or locoregional therapy (Liang et al., 2013). Systemic therapy, such as chemotherapy, is used along with liver-directed therapy in most patients with hepatic metastases.

Blood flow to the liver is delivered via the hepatic artery and the portal vein. The hepatic artery delivers oxygenated blood to the liver, and the portal vein collects the venous flow from the prehepatic splanchnic vascular bed. The hepatic artery perfuses liver metastases greater than 2–3 mm in size, and the normal liver cells receive the majority of their blood supply from the portal vein (Callahan & Kemeny, 2010; Kanat, Gewirtz, & Kemeny, 2012). Because most liver metastases receive a specific blood supply, this allows for targeted liver chemotherapy.

Methods

A literature search was conducted to identify a comprehensive range of relevant publications. Databases searched included CINAHL®, PubMed, Scopus, Google Books, and ProQuest Dissertations and Theses. The following key words and medical subject heading (MeSH) phrases were used: liver metastases, hepatic artery infusion pump, and chemotherapy pump. The search was limited to accessible full-text research articles, review articles, books, and expert content (textbooks) in English. The search dates were not limited but ended January 1, 2015, and disciplines outside of nursing were sought. Inclusion criteria included mention of hepatic artery infusion pumps (HAIPs) as single- or multimodality treatment of liver metastases from solid tumors and primary liver tumors. Literature regarding
intra-arterial chemotherapy and hepatic ports were not included in the review. All relevant literature available in the previously mentioned databases was reviewed.

Results

Database searching resulted in 511 titles and abstracts. After removal of duplicates and nonrelevant titles, 65 articles remained and were read in full (see Figure 1). Of these, 20 articles were excluded because they did not fit the inclusion criteria or did not focus on implantable HAIPs.

Discussion

Hepatic artery infusion of chemotherapy started in the 1960s. Initially, the catheter in the hepatic artery was connected to external infusion pumps (Callahan & Kemeny, 2010). Treatment with external pumps required close observation and was associated with numerous complications, such as thrombosis, bleeding, infection, and migration of the catheter (Callahan & Kemeny, 2010). A catheter connected to a subcutaneous port was developed in the 1960s, and this port could be accessed intermittently or continuously (Callahan & Kemeny, 2010). This approach had significant rates of hepatic artery thrombosis (Callahan & Kemeny, 2010) and was abandoned. In the 1970s, an implantable device was developed that delivered continuous chemotherapy to the liver. Complication rates declined with this pump but still include arterial thrombosis, catheter occlusion or dislodgement, extrahepatic perfusion, and pump pocket infection or hematoma (Callahan & Kemeny, 2010; Ko & Karanicolas, 2014). The use of hepatic artery infusion is limited to a few specialized centers in the United States and Japan because of the highly technical expertise for pump insertion and maintenance, as well as chemotherapy dose modification (Ko & Karanicolas, 2014).

Patient Selection

Candidates for consideration for the HAIP must have disease confined to the liver, sufficient hepatic and renal function (Ang et al., 2015), and vascular anatomy amenable to pump placement. Candidates for insertion of the HAIP include patients with single hepatic lesions or multiple hepatic lesions who are not eligible for surgical resection. Patients with portal vein thrombosis are excluded because of the high risk of hepatic ischemia (Callahan & Kemeny, 2010). An arteriogram is obtained prior to surgery to identify any aberrant hepatic vasculature because one-third of patients will have aberrant vascular anatomy (Callahan & Kemeny, 2010). Aberrant anatomy may require a different surgical approach for pump placement. The catheter is usually placed in the gastroduodenal artery (Callahan & Kemeny, 2010). A cholecystectomy is performed at the same time as pump placement to prevent chemotherapy-induced cholecystitis (Kanat et al., 2012).

Mechanism of Action

Hepatic artery infusion has advantages over IV therapy mainly because chemotherapeutic agents can be delivered specifically to malignant cells. When chemotherapy is administered intravenously, a fraction of the drug reaches the liver (Barber & Fabugais-Nazario, 2003). With hepatic artery infusion, higher first-pass hepatic drug concentrations can be achieved at the tumor site, exposing the metastatic cells to levels of drug that cannot be delivered systemically because of toxicity (Barber & Fabugais-Nazario, 2003). This is done while reducing systemic exposure and side effects (Barber & Fabugais-Nazario, 2003; Liang et al., 2013). For drugs with a steep dose-response curve, this may result in greater antitumor activity (Barber & Fabugais-Nazario, 2003). Studies have shown statistically significant differences (months, on average) in survival in those with unresectable metastatic colorectal cancer when hepatic artery infusion is used with or without concurrent systemic chemotherapy (Ko & Karanicolas, 2014). In cancers other than metastatic colorectal cancer, no outcome data exist regarding use of the HAIP as a single modality versus multimodality.

Procedures

Implantable HAIPs are placed during a laparotomy in the operating room. The hepatic and gastroduodenal arteries are identified. The hepatic artery is canulated by passing the catheter into the gastroduodenal artery to the hepatic artery (Barber & Fabugais-Nazario, 2003). The catheter is attached to the implantable pump, which is located in a surgically created subcutaneous pocket on either side of the rib cage and sutured to the fascia (Barber & Fabugais-Nazario, 2003; Martin, 2002). A cholecystectomy and total devascularization of the distal stomach and proximal duodenum is often performed to minimize the risk of drug-induced cholecystitis and misperfusion (Barber & Fabugais-Nazario, 2003; Ottery, Scupham, & Weese, 1986). A methylene blue-dye study is performed to verify hepatic uptake and absence of extrahepatic perfusion (Martin, 2002). A nuclear hepatobiliary scan is performed postoperatively to assess pump placement, hepatic flow, and verify absence of extrahepatic Thrombosis are excluded because of the high risk of hepatic ischemia (Callahan & Kemeny, 2010). Different surgical approaches are used in the management of HAIPs, including a surgical approach for pump placement. A cholecystectomy is performed at the same time as pump placement to prevent chemotherapy-induced cholecystitis (Kanat et al., 2012).

FIGURE 1. Literature Search Results
flow. Heparinized saline is placed in the pump at the time of surgery, and the pump is refilled with chemotherapy per the discretion of the surgeon based on liver function tests.

Clinical trials are exploring the safety and efficacy of HAIP placed via interventional radiology versus in the operating room, which is more surgically invasive (Sinn et al., 2013). Results from a phase II trial found that the pumps could be safely implanted via interventional radiology for primary liver tumors (Sinn et al., 2013).

**Hepatic Artery Infusion Pump**

The pump is divided into an inner and outer chamber. The inner chamber of the pump has a constant flow and provides stable drug dosing (see Figure 2). This reservoir is filled with either heparinized saline or chemotherapy through the septum, which is in the raised center. The pump will only hold enough medication for 14 days and will need to be refilled on day 14. Otherwise, the pump can run dry or become clotted. Glycerin is instilled in the pump when it is not being used for chemotherapy, which allows refills every six weeks. The outer pump chamber contains a propellant that forces the inner chamber contents through the catheter to the site of delivery as it is warmed by the body. The pump is pressurized by gas and will never need to be replaced (Martin, 2002). The pump catheters are placed directly within the hepatic artery or into the gastroduodenal artery. The pump itself is located above the muscle layer in the lower right abdomen. If the patient is morbidly obese, the pump may be placed above the muscle layer near the ribs for easier accessibility.

**Chemotherapy Agents**

The use of chemotherapeutic agents varies in the treatment of breast, uveal melanoma, and gastrointestinal cancer metastases. 5-Fluorodeoxyuridine is often used because of its short half-life (less than 10 minutes) and extensive first-pass extraction by the liver (94%-99%), which results in a 100–400-fold estimated increase in hepatic exposure (Kanat et al., 2012). In the United States, 5-fluorodeoxyuridine is used most often for hepatic artery infusion, whereas 5-fluorouracil, which yields only a 5-10-fold increase in hepatic exposure, is used in Europe and Japan (Kanat et al., 2012). Dexamethasone (20 mg) can be added to 5-fluorodeoxyuridine to reduce hepatotoxicity and increase efficiency (Kanat et al., 2012).

**Implications for Practice**

- Know the mechanisms of action of hepatic artery infusion pumps and how to care for patients with these pumps because of their increasing popularity in treating liver metastases.
- Educate patients regarding frequency of chemotherapy fills, implications if a scheduled fill is missed, and side effects that need to be reported to their healthcare providers.
- Become familiar with the protocol of administering and accessing the pump for chemotherapy fills.

Chemotherapy dose may be adjusted for renal and hepatic insufficiency. For any chemotherapy holidays, the pump may be filled with heparinized saline. With long-term chemotherapy holidays, the pump may be filled with glycerin every eight weeks. Depending on institutional policies, glycerin needs to be ordered about a week ahead of time because it is made by a compounding pharmacy.

**Implications for Nursing Practice and Patient Education**

The patients are given an identification card to carry while they have the HAIP for use in emergency departments, airports, and other security areas (Barber & Fabugais-Nazario, 2003; Martin, 2002) (see Figure 3). The company that makes the pump should be contacted to verify whether the patient can undergo magnetic resonance imaging or go through metal detectors. Patients should be instructed to avoid rough physical activity and lifting heavy objects (Barber & Fabugais-Nazario, 2003; Martin, 2002). This can flip the pump in the subcutaneous pocket or cause herniation, which compromises the efficacy of the pump and ability to access the device. When traveling in a plane, patients should check with their healthcare providers because pressure changes in the cabin can cause medication to flow faster (Barber & Fabugais-Nazario, 2003). Warm activities, such as using heating pads, electric blankets, hot water bottles, hot baths, saunas, or hot tubs, as well as getting sun exposure, should be avoided because they can raise a patient’s body temperature and cause the medication in the HAIP to flow faster because of an increase in vapor pressure in the pump, which directly increases the flow rate (Barber & Fabugais-Nazario, 2003; Cozzi, Hagle, McGregor, & Woodhouse, 1984).
To access the pump, a refill kit provided by the manufacturer needs to be obtained. Two different types of needles are used in HAIPs: a single-beveled bolus needle and a non-coring refill needle. A bolus needle should never be used without prior authorization of the prescribing provider because it will give the full dose of chemotherapy at the time of injection (Codman and Shurtleff, Inc., 2002). The pump is filled in a sterile environment and requires the use of sterile gloves and sterile field (Martin, 2002). Chemotherapy should be verified by two nurses according to institutional chemotherapy administration guidelines. The area around the pump is prepared with Betadine swabs followed by an alcohol swab. The non-coring needle is attached via stopcock valve to a syringe (Codman and Shurtleff, Inc., 2002) and then placed into the diaphragm of the pump. Verification of correct placement is the visualization of fluid passively entering the syringe (Codman and Shurtleff, Inc., 2002). Documenting the amount of fluid that is removed from the pump is important because it assists the physician in prescribing future doses of chemotherapy (Codman and Shurtleff, Inc., 2002). After the pump has been accessed, gloves should be changed in accordance with evidence-based chemotherapy administration guidelines (Neuss et al., 2013). Once the fluid has stopped flowing from the pump, the syringe can be disconnected from the closed system and disposed of in a chemotherapy-approved container. The syringe with chemotherapy is attached to the closed system and slowly injected into the pump. A blood return will not occur; however, placement can always be verified by visualizing the chemotherapy coming out of the pump and back into the syringe if pressure from the syringe is released (Codman and Shurtleff, Inc., 2002). Once all of the chemotherapy is instilled, the needle can be removed from the patient, and the closed system can be discarded into a chemotherapy-approved container. An adhesive dressing can be applied over the needle insertion site (Codman and Shurtleff, Inc., 2002). The patient does not have to enact chemotherapy-medication precautions and will return home after the instillation.

Patients should be instructed to contact their healthcare providers for fevers of 100.4°F or greater or redness, tenderness, or drainage at the insertion site (Barber & Fabugais-Nazario, 2003). Any swelling at the insertion site should also be reported. If patients are unable to keep a pump fill appointment, they must contact their healthcare providers to reschedule the appointment as soon as possible to prevent the pump from clotting or running dry and causing pump failure (Barber & Fabugais-Nazario, 2003). The Codman® 3000 implantable pump is the only available implantable HAIP available in the United States. The company provides a 24/7 nurse information line, which can be used to troubleshoot difficulties with the pump. In addition, the company has a phone number patients can access if they are having difficulties or have questions regarding the pump.

Conclusions

Hepatic artery infusion can be combined safely with systemic chemotherapy in neoadjuvant, second-line, and adjuvant treatment of selected patients (Kanat et al., 2012; Liang et al., 2015). For patients with hepatic metastases, hepatic artery infusion is an option for malignancies that have a poor response to systemic chemotherapy, such as melanoma and pancreatic cancer.

What care will the pump need?
The pump will need to be refilled about every two weeks to make sure there is always fluid in the pump. Each time the pump is filled, all of the old medicine is removed, and new medicine is inserted. The flow rate of your pump will be checked every time this is done to make sure you are getting the correct amount of medicine each time. The pump flow rate can change depending on pressure and temperature. You may be asked to stop doing some activities to prevent a big change in the flow rate.

Are there any activities that I should not do after the pump is in place?
After you recover from your surgery, you will be able to do most of the activities you did before the pump was put in, but there are some that you should not do. It is very important that you tell your doctor if you are having fevers.

Activities that you should not do include

- Playing rough or doing contact sports that could hurt the pump.
- Deep sea or scuba diving; these cause increased pressure that could change the flow rate. You can swim or snorkel.
- Using a heating pad or water bottle on the pump area. The heat can increase the flow rate.
- Spending time in a sauna or hot tub. The heat can increase the flow rate.

What happens if I miss an appointment?
It is very important to keep your appointments to make sure your pump is working correctly. If you are unable to keep your appointment, call the office right away to make other arrangements.

Can I have magnetic resonance imaging (MRI)?
The company that makes the pump should be contacted to verify whether you can undergo MRI.

Can I have blood drawn through the pump?
This pump has a very special, specific use. Blood cannot be drawn from the pump or port. The pump should never have pressure applied to remove fluid or blood. This could damage the pump. Only specially trained doctors and nurses should work with this pump.

Can I get other IV medicine, like anti-nausea medicine, through this pump?
Only certain medicines are safe to give through this special pump. Only a doctor who has experience with this type of pump should prescribe medicines to be given using the pump.

Can I travel with the pump?
Let your doctor know if you are traveling by airplane or if you are changing elevation because the pressure can change the flow rate. The doctor may need to change the schedule to refill your pump to make sure you have plenty of medicine in the pump when you travel or do anything that could change the flow rate.

Will the pump set off airport security systems?
It is unlikely that the metal would be detected, but it is important for you to always carry the patient identification card you are given when the pump is placed. The information on the card will help security understand what the pump is used for, and it will also help others know what to do in case you have an emergency that requires medical care.

FIGURE 3. Example of a Patient Information Sheet

Note. Figure courtesy of the Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. Used with permission.
Careful patient monitoring and patient education is vital to the success of this treatment.

References


