Perioperative considerations in the oncologic patient undergoing isolated limb perfusion

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Abstract

Isolated limb perfusion (ILP) and hyperthermic ILP (HILP) are therapeutic options for patients with unresectable malignancies in the extremities (e.g., primarily melanoma and soft tissue tumors), they induce a high rate of tumor response; associates with high limb salvage rates and represents an effective alternative to amputation. These are challenging procedures with a high technical difficulty that require the efforts of a multidisciplinary team (surgeon, anesthesiologist, nurse, perfusionist and intensivist). Hemodynamic changes, drug leakage through collateral vessels, local and systemic toxicity, and potential complications require continuous and invasive monitoring during the procedure and rigorous post-surgical monitoring. The purpose of this review article was to update the strategies for the perioperative care of cancer patients undergoing this procedure.

Key words: Isolation perfusion cancer chemotherapy. Regional perfusion antineoplastic chemotherapy. Perioperative care. Anesthesia.

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Introduction

Isolated perfusion was described in 1957 by Ryan et al.¹ in experimental models, which had the purpose to maintain an elevated concentration of chemotherapeutic agents within the limits of a tumor and thus reduce the risk of systemic toxicity by means of arterial and venous catheterization of a region and its connection to an extracorporeal circulation system². On next year, isolated limb perfusion (ILP) application clinical results were presented in 1958 by Creech et al.³ and, subsequently, the same group⁴ reported the results of the first phase II study. In 1969, Stehlin⁵ proposed the use of hyperthermia (HILP) as an additional strategy to potentiate the cytotoxic effect, improve antitumor response and avoid dermal and subdermal beds vasoconstriction.

Ever since, it has been successfully used in the treatment of neoplasms in the extremities, such as soft tissue sarcomas and melanoma⁶⁻¹¹, although it has also been described in tumors with other localization such as the liver, stomach and colon, pelvis, the maxillofacial region, and head and neck¹²⁻¹⁶. Currently, not only chemotherapeutic agents are perfused (e.g., melphalan¹⁷), but also immunotherapeutic drugs (e.g., tumor necrosis factor α [TNF- α]^{18,19}).

The procedure accomplishes limb salvage in 74-87% of patients and in up to 71% of those who would otherwise have been treated with amputation, resection and radiotherapy². Complete tumor remission has been reported to range from 17 to 75%, and partial remission, from 25 to 64%, according to the type of tumor and the modality of isolated perfusion applied²⁰⁻²⁵.

ILP and HILP are complex surgical techniques that require close collaboration between the surgical oncologist, the anesthesiologist, the perfusionist and the nurse²⁶. In this review, current evidence on the perioperative management of patients undergoing this procedure is summarized.

Procedure

The surgical procedure is performed under general anesthesia and with invasive monitoring by means of central venous catheter and arterial line. Blood circulation isolation of the extremity with regard to systemic circulation is carried out after dissection, clamping and catheterization of a portion (4-5 cm) of its main vessels (artery and vein), and ligation of collateral vessels and, finally, application of a pneumatic tourniquet (at

250-mmHg pressure) in order to occlude muscle and cutaneous capillary vessels^{1,2,9,27,28}.

Artery and vein catheterization enables the connection of a circulation and oxygenation extracorporeal circuit (perfusion pump, oxygenator and heat exchanger) (Fig. 1). Priming is made with 700-1000 mL of a balanced electrolyte solution, a red blood cell concentrate and heparin. The temperature at which the extremity will be perfused (ILP or HILP) is assigned with normothermia (37-38 °C), mild hyperthermia (39-40 °C), borderline true hyperthermia (40-41 °C) or true hyperthermia (41-43 °C). Maintaining the extremity below 41.5 °C is recommended, since a temperature above this figure is associated with higher regional toxicity^{29,30}. Similarly, regulating the flow is recommended at rates of 400-500 mL/min and 150-300 mL/min for lower and higher extremity, respectively, since a higher flow increases the possibility of local circulation leakage and development of systemic effects^{31,32}.

Next, the drugs are administered (Table 1), with perfusion being maintained for 60-90 min. The medication doses are calculated in relation to the volume of the extremity, and to calculate it, the displacement method can be used, where the extremity is submerged in a calibrated cylinder filled with water and the volume of displaced fluid is determined, or else by performing the calculation based on a modification of the cylinder volume formula by measuring the length and circumference of the extremity at multiple points.

The development of chemofiltration techniques has enabled that the passage of venous blood through a filter removes excess of drugs and avoids local toxic effects and the possibility of systemic effects in anatomical regions that are difficult to fully isolate^{9,33}.

Still, the detection of leaks into the systemic circulation is essential and, for that, iodine 131-marked albumin or technetium 99-marked red blood cells and a gamma probe or gamma camera are used in the precordial region. Losses lower than 1% can be detected with this method^{34,35}; in the case of leaks > 5%, interrupting the procedure is recommended owing to the risk of systemic toxicity¹⁷.

Once the drugs have been administered, the perfusion is concluded by washing the perfusate out with saline and dextran (Haemacel®) or saline and red blood cell concentrate; the circuit is interrupted, the perfusion pump is disconnected, the tourniquet is deflated and the cannulas are removed. Subsequently, the blood vessels are repaired in order for blood flow to the extremity to be reestablished³².

Figure 1. Isolated perfusion circuit (adapted from Verhoef et al.⁵³).

Table 1. Doses of drugs used in ILP and HILP

Drug	Dose
Melphalan	Lower limb : 10 mg/L Upper limb: 13 mg/L
Doxorubicin	10-18 mg/L
Soxorubicin	8.5 mg/L
Cisplatin	20 mg/L
Actinomycin D	50-100 µg/L (usually 75 µg/L)
TNF- α	Upper limb: 1-3 mg Lower limb: 1-4 mg
Interferon- γ	0.2 mg

Performing a prophylactic closed fasciotomy of the anterior compartment of the leg or of the ventral and dorsal compartments of the forearm has been suggested in order to prevent the development of compartmental syndrome; however, given that the incidence of this complication is lower than 5%³⁶⁻³⁹, the procedure can be carried out if postoperative clinical evolution warrants it, or if an increase in intracompartmental pressure directly measured through a monitor is reported⁴⁰.

Blood volume

Blood volume changes should be invasively and proactively monitored and with immediate response by the anesthesiologist. Losses can be estimated through the volume required to maintain mean blood pressure. In medical literature, there is an extremely wide range reported of both loss of blood (up to 3 L) and loss of intravenous fluids used for replacement (up to 13 L)²⁶; therefore, insertion of one or two large caliber (14 or 16 G) central venous catheters is recommendable, as well as having three to five red blood cell concentrate units available for each patient.

The choice between the use of colloid and crystalloid solution during ILP or HILP intraoperative fluids management is, as in other fields of anesthesia, part of the scientific debate^{41,42}. The use of colloids such as 6% iso-oncotic hydroxyethyl starch or other solutions, which are related to shorter time and lower administered volume, can be considered in order for hemodynamic stabilization to be achieved. Unlike previous data, more recent studies have demonstrated that they are not associated with an increase in mortality or deterioration of the renal function^{43,44}.

Anesthesia

ILP and HILP involve major surgery and are therefore carried out under general anesthesia and with orotracheal intubation. Owing to the need of systemic heparinization, regional and epidural anesthesia are not recommended³². Premedication is provided with midazolam (1-2 mg), to subsequently carry out induction with propofol (1-2 mg/kg), fentanyl (0.5-1 µg/kg) and rocuronium (0.6 mg/kg) for neuromuscular blockage²⁶. Other authors report the use of thiopental and nitric oxide⁴⁵. After intubation, anesthesia is maintained with isoflurane, desflurane or sevoflurane with fraction of inspired oxygen (FiO₂) between 0.5 and 1.0. Subsequent doses of fentanyl and/or neuromuscular blocker are administered. At the conclusion of the procedure, gas administration is interrupted and, after neuromuscular blockage reversion, patient extubation is carried out.

Hemodynamic changes

Hemodynamic monitoring includes heart rate, systolic and diastolic blood pressure, mean blood pressure, central venous pressure, urine output, temperature, estimated blood loss and the volume of transfused blood products and administered fluids. Important hemodynamic changes are observed during ILP and HILP. Different authors have reported a decrease in mean blood pressure, as well as in the shock index (heart rate/systolic blood pressure), at different moments of the procedure²⁶.

These changes may be due to the isolation of the extremity in the perfusion circuit, leaks of the perfusion circuit volume to systemic circulation and vice versa, to blood losses, to the patient's cardiac reserve and previous cardiac status, to ischemia-reperfusion phenomena and even to the pharmacologic effect of some agents such as TNF-α.

TNF-α side effects are generally dose-dependent and comparable to the systemic and hemodynamic alterations of septic shock (e.g., tachycardia, hypotension, peripheral vascular resistance decrease, cardiac index increase, coagulopathy, thrombocytopenia, hepatocellular damage and even multiple organ failure^{32,46}). In addition to monitoring, fluid replacement, blood products' administration and, if required, vasoactive amines administration is recommended.

Postoperative complications

ILP and HILP complications are grouped as local and systemic. The former were classified by Wieberdink et

al. in 1982 in a five-grade scale, which is standardly used ever since (Table 2)⁴⁷. In the majority of studies, a predominance of grade I (no reaction) and grade II toxicity (erythema and mild edema) is reported, with an incidence ranging from 32 to 100%, whereas grade III toxicity occurs less frequently (1 to 19%)^{36,37,48-53}.

High-grade toxicity requiring management with fasciotomy for compartmental syndrome (grade IV) or amputation for tissue loss and necrosis (grade V) has been reported in 1-2% of patients^{37,54,55}.

After surgery, elevation of the intervened extremity is recommended, which can contribute to reduce edema and enables better assessment of the limb compartments. Some authors report the practice of daily monitoring of serum creatine kinase levels to early determine the presence of muscular toxicity. Significant elevation of this enzyme (> 1000 mg/L) can indicate the need for prophylactic administration of systemic steroids⁴⁰.

The diagnosis of compartmental syndrome is essentially clinical, and it requires immediate management with fasciotomy; however, postoperative follow-up can be supported by intra-compartmental pressure monitoring^{40,56}. Monitoring for at least 24 h is recommended or until a consistent pressure decrease and pressure differential increase is observed⁵⁷.

Pain and local discomfort occur in 25-40% of patients but, as other local complications, they usually resolve in about 2-3 weeks^{32,58}.

Neurotoxicity can manifest itself by stabbing pain and paresthesia, the onset of which is 2-3 weeks after the procedure, and is also reported in 25-40% of patients; usually, it resolves in a few months. Long-lasting neuropathy is much rarer (1-4%)^{32,58}.

Vascular complications occur less frequently. Incidence of thrombosis at the arteriotomy site has been reported in 2.5%, while deep venous thrombosis is

Table 2. Wieberdink classification of post-ILP regional toxicity⁴⁷

Grade	Description
Grade I	No subjective or objective evidence of reaction
Grade II	Mild edema and/or erythema
Grade III	Considerable edema and/or erythema with some blistering, slight mobility alteration
Grade IV	Extensive epidermolysis and/or evident damage to the deep tissues, causing definite functional disability, manifest or imminent compartmental syndrome
Grade V	Reaction that may necessitate amputation

close to 10%, in spite of heparinization during the procedure. In the latter, the tumor thrombogenic effect, cytotoxic drugs, surgical trauma, edema and decreased mobility do intervene^{32,58}.

Systemic complications are mainly related to effects of the drugs that may happen to leak from the perfusion circuit during the procedure. Even under conditions of perfect isolation of the extremity and adequately washing the drugs out prior to finalizing the procedure, certain amounts of them can remain in the perfused extremity tissues or in the intravascular compartment and, from there, redistribute when systemic circulation is reestablished. In consequence, transoperative and postoperative surveillance is extremely relevant.

Melphalan and other cytostatic drugs can produce allergic reactions, cardiorespiratory arrest, neutropenia and other alterations of the hematopoietic system²⁶. Nausea and vomiting occur within the first 24 h after the procedure and are easily managed. One study demonstrated 13% of grade I, 4% of grade II and 0% of grade III in the World Health Organization scale^{59,60}.

TNF- α can lead to an inflammatory response syndrome (similar to septic shock) that is accompanied by fever, increased cardiac output, systemic vascular resistance drop and need of resuscitation with fluids and inotropic agents, and the intensity of this reaction is dependent on the dose and on the intensity of the leakage to systemic circulation, with a duration that can be of up to 24 h after the perfusion^{2,23,39,61}. One study where the systemic concentration of this agent was measured, found that higher levels were associated with the development of multiple organ failure⁶².

Conclusions

ILP and HILP are safe procedures that induce a high rate of tumor response and achieve an elevated rate of limb salvage; therefore, these techniques represent an alternative to amputation when local disease control is necessary. Although their first description occurred halfway through last century, these techniques have been improved with the addition of new drugs during the perfusion such as TNF- α , interferon, and even gene therapy. However, elevated technical difficulty, hemodynamic changes and possible complications require multidisciplinary intervention of the surgeon, the anesthesiologist, the perfusionist technician, the nurse and the intensivist.

Conflict of interests

The authors declare not having any conflicts of interests relevant to this manuscript.

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