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HOW I DO IT

A Safe and Fast Technique for Isolated Hepatic Perfusion

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INTRODUCTION

Isolated hyperthermic antiblastic perfusion of the liver is currently gaining acceptance among surgeons and oncologists as a treatment for multiple unresectable liver metastases when conventional chemotherapy failed to halt progression of the disease [1]. Currently, new promising drugs are under investigation to further improve the efficacy of the treatment [2]. Colorectal cancer is the most sensitive histology to such a therapy [3] but other primary tumors seems to benefit as well [4–6].

Herein we describe our modified technique of isolated hepatic perfusion that is simpler and faster compared to the initial ones reported in the literature. Previous techniques [7] of isolated hepatic perfusion included total vascular isolation of the liver with portal and systemic venous by pass. The venous by pass was performed either using a cut-down technique or by percutaneous cannulation of the femoral vein. Another important step of previous described techniques was the continuous intra-operative monitoring of complete vascular isolation of the liver by 131-I labeled serum albumin. The technique we describe herein does not include portal vein by pass but shunting of the blood is limited solely to the inferior vena cava. Complete vascular isolation of the liver is demonstrated by a steady volume of the reservoir during the entire procedure, without using labeled albumin.

SURGICAL TECHNIQUE

The patient is placed in the supine position and general anesthesia through orotracheal intubation is provided. The patient is invasively monitored by radial artery catheter and Swan-Ganz catheter in the pulmonary artery. An 18-French cannula is also placed in the right jugular vein (right if possible) for veno-venous by-pass (see below).

The operation begins with a mini-laparotomy on the midline to asses the feasibility of the operation. Once peritoneal carcinomatosis or massive extra-hepatic neoplastic disease is ruled out, the midline incision is extended up to the xyphoid process and to a subcostal laparotomy. The quality of the liver is assessed, with special attention to the steato-hepatitis following chemotherapy. In case of severe steatosis the procedure is not indicated due to increased risk of liver failure after the perfusion.

The liver is fully mobilized by division of the right and left triangular ligaments, the round ligament and all the retroperitoneal attachments.

The vena cava is dissected off the retroperitoneum and attention is paid to ligate and divide all the collateral veins from the retroperitoneum. The adrenal vein is also tied off and divided. The infra-hepatic inferior vena cava is encircled with an umbilical tape and a Rumel tourniquet is secured around this portion of the cava. This tourniquet will provide inferior vena cava exclusion from the systemic circulation without occluding a cannula that is inside the caval lumen (circuit 1, see Fig. 1). The supra-hepatic inferior vena cava is also freed and encircled.

The hepatic hilum is dissected and all the elements of the porta hepatis are identified. The gastroduodenal artery (GDA) is freed and encircled. It is important to ligate all possible collaterals from the GDA to avoid any leak of the infused drug. The gallbladder is removed to prevent post-treatment cholecystitis.

At this point of the operation, the patient is systemically heparinized (200 U/kg are given). The right femoral vein is percutaneously cannulated with 18-French cannula (50-cm in length). The cannula is pushed into the inferior vena cava and placed just below the supra-hepatic veins. This cannula will provide the only liver outflow during the hepatic perfusion (see below). The left femoral vein is also percutaneously cannulated with an 18-French cannula (18-cm in length) and introduced into the saphenous vein. The distal tip of this cannula is placed just below the renal veins. This cannula will be connected with the veno-venous by-pass and will provide blood return to the jugular vein during the extracorporeal by-pass (circuit 2, see Fig. 1).

It is our preference to cannulate the saphenous veins percutaneously as routinely done in our practice for liver transplantation. This practice is associated with a lower incidence of post-operative complications such as lymphocele.

The GDA can now be cannulated. The distal end of the GDA is ligated with a 2/0 silk tie. A transverse arterotomy is performed and an arterial catheter (3 mm) is inserted into the artery close to the hepatic artery take off to assure the both lobes of the liver will be perfused. A vascular clamp is placed at the hepatic hilum occluding the common hepatic artery (proximally to the cannulated GDA), the portal vein and the bile duct (see Fig. 2). The infra-hepatic vena cava is occluded with the Rumel tourniquet tied around the inserted cannula. The supra-hepatic vena cava is occluded with a curved vascular clamp (for this purpose, we use the same instrument used in liver transplant surgery). The only inflow to the liver occurs through the arterial catheter placed in the GDA and the only outflow from the liver is through the cannula placed just below the supra-hepatic veins (see Fig. 1).

Two needles are inserted in the right and left lobe of the liver and connected to a temperature probes of the heat exchanger.

The perfusion of the liver is provided by the extracorporeal circuit 1 where the blood is pushed into the liver by a roller pump. The

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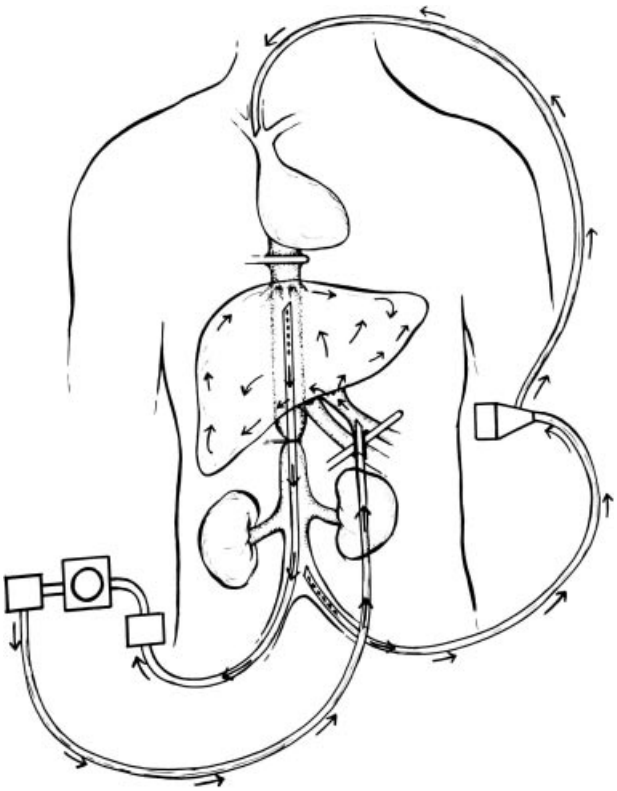

Fig. 1. The drawing shows the scheme of our technique of isolated hepatic perfusion. Circuit 1 is the perfusion system and circuit 2 is the systemic by pass. The hepatic hilum is clamped and no portal by pass is provided.

extracorporeal circuit 2 is the veno-venous by-pass. It is represented by a centrifugal pump and provides patient's hemodynamic stability during cava clamping.

At this time the perfusion can start.
The veno-venous bypass will be initiated first and flow stabilized at 1.8–3.0/min.
Next, the inferior vena cava is clamped by tying the Rumel tourniquet.

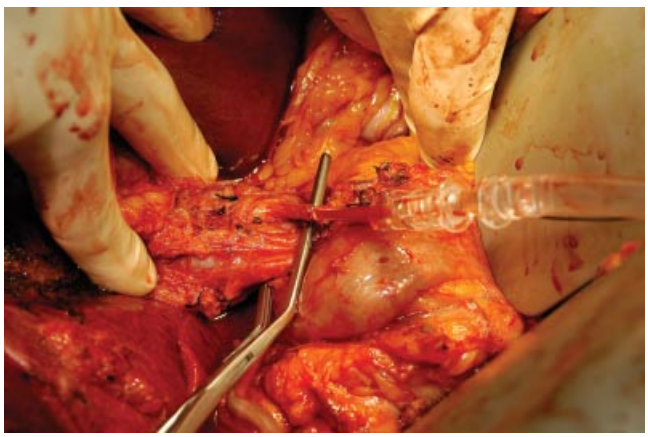

Fig. 2. The picture shows clamping of hepatic hilum. The distal gastroduodenal artery (GDA) is cannulated, the proximal portion is tied. The vascular clamp encompasses the bile duct, portal vein and the hepatic artery proximally to the take off of the GDA.

The following step includes clamping of the hepatic hilum. Finally, the supra-hepatic vena cava is clamped with the curved vascular clamp to achieve a complete vascular isolation of the liver.

The GDA cannula is connected with the liver perfusion circuit (circuit 1) and a priming solution (consisting of 700 ml of normal saline, 300 cm^3 of packed red blood Cells and 50 mEq of sodium bicarbonate), begins to circulate. The sodium bicarbonate is added to keep a pH of the priming solution around 7.32.

The correct functioning of the circuit 1 is verified before the infusion of the chemotherapeutic agent is started.
The flow is regulated to range from 800 to 1,200 ml/min.
The circuit pressure must be around 150–250 mm Hg.
If a deviation from these values is observed the surgeon has to reposition the cannula or change the angle of the tubing of the circuit.
The integrity of the circuit 1 is also assessed. Reservoir volume must be steady (meaning no leak of perfusate through the general circulation).
The temperature of the perfusate is regulated by the heat exchanger to reach 41°C in the liver parenchyma as shown by the needles probe implanted in the liver.

At this point the selected drug can be added to the circuit. Currently we use melphalan is 1.5 mg/kg of patient ideal body weight. Oxaliplatin dose is 40 mg/m^2. The oxaliplatin dose is still under investigation and could change in a near future [2].

After 60 min of perfusion the wash out procedure begins. Normal saline (1,500 cm^3) is added to the reservoir, then the inflow line to the reservoir is closed and all the fluid coming from the liver is wasted through the drain line in an appropriate container.

When a clear perfusate is achieved, the veno-venous by-pass is interrupted. Then the following sequence of steps takes place and the circuits are interrupted by releasing of all the clamps.

The percutaneously placed cannulas are removed and pressure is exerted at the puncture site to secure hemostasis.

The gastroduodenal arterial cannula is removed. It is our preference to leave in place a catheter connected to a pump for intra-arterial chemotherapy.

RESULTS

Ten patients undergoing isolated hepatic perfusion at our Institution with this technique are presented herein.

Patients tolerated the procedure well without hemodynamic instability. There was no operative mortality and one intra-operative complication (one accessory hepatic artery could not be cannulated).

Intra-operative blood loss was within the range of a major liver surgery: mean 750 cm^3 of blood (see Table I). Mean Operating Room time was 438 min. Other intra-operative parameters are reported in Table I. Post-operative complications were: pleural effusion (4 pts), bleeding at the pump insertion site (1 pt) diaphragmatic relaxation (1pt) (see Table II). Of note, none of our patients developed an overt liver failure.

One patient experienced a striking increase in the transaminases and bilirubin levels due to massive lobar necrosis (see Fig. 3) but he completely recovered after a week. There was no post-operative mortality in our series.

White blood cells and platelets count, Hematocrit, and renal function have always been in a range consistent with major surgery, and absence of systemic toxicity.

DISCUSSION

Isolated hepatic perfusion is performed increasingly for palliation of patients with unresectable liver metastases from different histolo-

TABLE I. Intra-Operative Parameters During IHP With the New Technique

Operating Room time	Mean 438.8 m (330–550 min)
Estimated blood loss	Mean 750 cm^3 (300–2,500 cm^3)
PRBCs (blood transfusion)	2.3 U (1–8 U)
IV crystalloids	8.8 L (3–17 L)
Fresh frozen plasma administered	4.1 U (3–8 U)
Reservoir volume	700 cm^3 (stable)
Venous–venous by pass flow	0.8–1.77 L/min

gies. The technique has been proven to be safe and partially effective for some individual histologies. Technical complexity along with lack of randomized clinical trial comparing IHP with chemotherapy, might still represent one of the major drawbacks of this procedure. An effort to simplify the procedure is therefore needed. Ideally, palliative procedures, such as IHP with a still unclear role in treating patients, should be safe, not time-consuming, with minor patient's derangement and not expensive. Our effort is to minimize the impact of the procedure on hospital cost and OR time and make isolated hepatic perfusion competitive with other forms of therapy such as the percutaneous one.

In our experience the procedure was faster and simpler compared to previous described techniques, due to the avoidance of continuous intra-operative 131-I human serum albumin leak monitoring. In such a system, a dose of labeled albumin is administered to the patient by intravenous injection. A gamma detection camera is needed similar to the one used for the isolated limb perfusion. The camera is positioned over the veno-venous by pass pump to measure a baseline counts per minute of the labeled albumin. Then a 10-time higher dose is injected into the perfusion circuit and any increase in the baseline counts per minute observed at the veno-venous by pass pump through the gamma detection camera, is assumed to indicate a leak from the perfusion system into the systemic circulation.

However, pharmacokinetic studies (see Table III) performed during a phase I trial with oxaliplatin ([2] and unpublished data from University of Pittsburgh) show no leak of perfusate during the procedure, no difference in drug distribution and absorption. We did not observe any leak of perfusate during the procedures, with the reservoir being stable in all the perfusions and no systemic toxicity observed post-operatively in our patient population.

Moreover, several papers [3,7] have reported a very low rate of leak into the systemic circulation, provided that cannulas are placed correctly and that the porta hepatis is securely clamped. With this in mind, we thought that a simple check of the reservoir volume would have been safe enough to perform the procedure without the use of labeled albumin. Changes in the reservoir volume reflects changes in the dose of the perfusate circulating through the liver perfusion circuit and ultimately, in the systemic circulation. Careful ligation of all the retroperitoneum vena cava collaterals and clamping of the hepatic hilum allows to achieve a complete vascular exclusion of the liver. Hepatic hilum clamping encompasses common bile duct, portal vein and the hepatic artery so that no escape of the drug can occur through the portal or biliary system. In our experience we did not observe any systemic toxicity of the patients as shown in Table III.

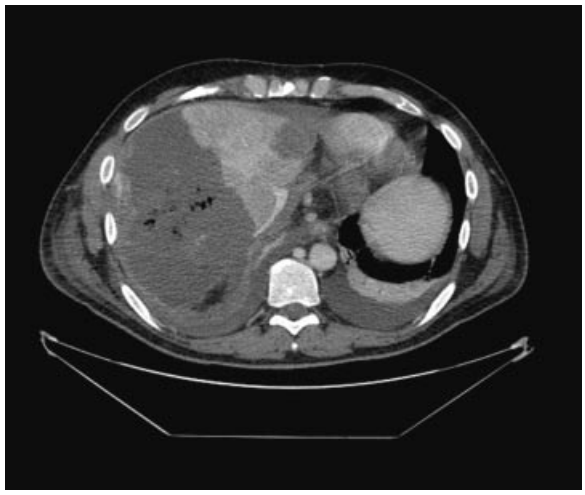

Fig. 3. The picture shows CT scan image of a right lobe necrosis. On the left lobe a necrosed metastases is also seen.

During the procedure patients have been hemodynamically stable without the portal by pass and clamping of the portal vein did not result in major swelling of the intestine or edematous changes. In our liver transplantation practice, we almost always perform vascular anastomoses without portal flow shunting. However in liver transplant patients one could expect venous flow through collateral because of the portal hypertension. Interestingly enough, our patients did not experience any trouble with portal vein being clamped for 60 min. Anesthesia management included generous fluid administration prior of clamping and, consistently with hemodynamic changes, careful positive fluid balance was maintained (see Table I).

Mean OR time was 7.3 hr, lower if compared to previous reported OR time [3,7].

With this technique, peri-operative mortality was absent and post-operative morbidity was minor, consisting of pleural effusion in the majority of our patients. The massive hepatic necrosis we observed was due to the peculiar surgical anatomy of the patient. The right hepatic artery was thrombosed because of previous surgery and we perfused the liver only through the left hepatic artery assuming that re-vascularization of the right lobe was occurred. However homogeneous liver perfusion was not achieved as demonstrated by the parenchymal necrosis of the right lobe (see Fig. 3).

TABLE II. Complications Experienced With This Technique

Patient	Sex	Age	Complications
1	F	27	Pleural effusion
2	M	29	None
3	M	43	Pleural effusion. Right liver lobe necrosis
4	F	45	None
5	M	60	Diaphragmatic relaxation and pleural effusion
6	F	52	Pleural effusion
7	M	51	None
8	M	61	None
9	F	59	Bleeding at subcutaneous pocket for pump
10	F	65	None

TABLE III. Summary of PCI Trial 02–135 Isolated Hepatic Perfusion With Oxaliplatin

Patient #	Dose (mg/m^2)	Perfusate oxaliplatin AUC	Serum oxaliplatin AUC
1	5	49.4	ND
2	10	81.8	ND
3	20	195	ND
4	40	388	ND
5	40	461	ND
6	40	466	ND
7	60	1,042	ND
8	40	461	ND
9	40	449	ND

In our experience, the procedures were overall simpler and faster compared to the previous used technique and, most of all, extremely safe.

CONCLUSIONS

Our technique of isolated hepatic perfusion is simpler and faster compared to the previous described technique and allows safe antiblastic perfusion of the liver, reducing time, and cost of the procedure. This new technique is not associated with an increase in intra-operative and post-operative morbidity and mortality. Complete vascular isolation can be achieved with a total clamping of the hepatic hilum. Hemodynamic stability can be provided with a careful anesthesia management during portal vein occlusion.

We do not recommend use of portal venous–venous by pass or continuous intra-operative leak monitoring anymore.

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