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CASE STUDY OF USE OF NONINVASIVE HEMODYNAMIC DOPPLER MONITORING IN HYPERTHERMIC INFUSED LIMB PERFUSION

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ABSTRACT

Hypothermic Infused Limb Perfusion (HILP) is treatment used for patients with metastatic melanoma of extremities which consist of delivering high concentrations of cytostatic drug to cancer of affected limb and at the same time avoiding systemic side effects of cytotoxic drug. Potentially life-threatening complication of this procedure is acute hypovolemia as outcome of fluid shift between vascular compartment of isolated limb and the systematic vascular compartment

Keywords: HILP, hemodynamic, Cardio Q, melanoma.



1. INTRODUCTION

Hypothermic Infused Limb Perfusion (HILP) is surgical technique of treating unresectable, recurrent metastatic melanoma and sarcomas of the extremities (1,2). Metastatic tumors are results of dissemination of the primary tumor from its source to the regional lymph nodes. HILP is based on the achievement of the synergistic action of hyperthermia and high concentrations of cytostatic agent in the tumor of extremities at the same time avoiding the systemic effect of cytostatics (2-4).

The operation consists of several parts: dissection of the lymph nodes unless it has been performed in previous surgical act. For upper limb it consists of removal of lymph nodes from levels I to III, and for the lower extremity superficial dissection is performed to the inguinal ligament or a deep dissection through retroperitoneal space. After lymph node dissection and clamping of side branches, artery and vein of extremity are exposed for cannulation - axillary artery and vein in the upper extremities or the femoral/iliac artery and vein in the lower extremity. Cannulated blood vessels are connected to the system for extracorporeal circulation with which performs the heating of the limb (until desired temperature is reached) and perfusion with cytostatic. After perfusion ends, the limb is washed out of existing blood with cytostatic and the surgical field is closed. The extracorporeal circuit contains a pump that warms the blood and allows delivery of cytostatics to cancer and oxygenator that provides sufficient pressure of oxygen in the blood before entering the legs or arms (1,3,5).

The combination of HILP and cytostatic melphalan gave a good response in 65-100% of patients, and complete response to therapy in 25-76% of patients (6).

This procedure carries potentially life-threatening complication such as acute hypovolemia (7,8). Due to this high risk operation, especially with serious hemodynamic changes, use of Cardio Q, device for non-invasive continuous hemodynamic monitoring (10,11) is required.

2. CASE STUDY

A woman aged 50 was admitted to the clinic for oncology surgery to treat the recurrence of malignant melanoma of the right leg using HILP technique. The patient had previously been performed excision of the right leg tumor and then re-excision of tumor recurrence.

Preoperative anesthetic evaluation was performed on the bases of the medical records, physical examination, complete blood count, biochemical analysis, assessment of liver function and kidney function, electrocardiogram (ECG) and X-ray of the lungs.

The patient had no associated comorbidities or was taking any therapy. All laboratory test results were satisfactory.

The patient gained insight about the anesthesia and the planned surgical treatment and gave written consent for the treatment.

Premedication was performed with 1-2 mg of midazolam and 0.5 mg atropine. The patient was placed on the air blanket and another air blanket was set over him. Prewarming was started 10 minutes before induction of anesthesia, heating the entire body with temperature of 40C⁰. After placement of intravenous cannula of 18G, the patient was introduced in anesthesia with propofol 2 mg/kg body weight (BW), fentanyl 1mcg/kg BW and rocuronium 0.8 mg/ kg BW to achieve neuromuscular blockade.

After orotracheal intubation an arterial line, central venous lines, esophageal Doppler probe for hemodynamic monitoring, nasogastric tube, temperature probe and a urinary catheter were placed. In addition, the second intravenous cannula of 16G for rapid fluid replacement was inserted and the patient connected to the device for rapid fluid replacement.

Non-invasive continuous hemodynamic monitoring device (The CardioQ cardiac output and fluid status monitoring system is manufactured by Deltex Medical Ltd.) is associated with esophageal Doppler probe. Esophageal Doppler probe is placed to level of descendent aorta and blood flow through it on the monitor screen shows the characteristic curve with clear sound effect, which ensures accurate setting of the probe. CardioQ esophageal Doppler monitor gives us the most important hemodynamic parameters for the accurate management of fluids: stroke and cardiac output, time flow, maximum flow rate, cardiac index, heart rate, and all this in real time, continuously, with each cardiac cycle. Circulatory changes are identified early, as soon as they occur, and the clinician can react appropriately timely to react by adjusting the fluids or appropriate medicines. Protocol of stroke volume optimization which is recommended in terms of Goal Directed Therapy, involves so-called "fluid challenge". That is test with a 200ml of fluid bolus, after which it follows the response the response follows. CardioQ provides continuous, so-called "beat to beat" monitoring response circulation to the test, to optimization until optimization and hemodynamic stabilization are completed.



The protocol of stroke volume optimization:

- After the initial administration of 200ml of liquid, stroke volume (SV) is measured
- If SV increase by 10% we stop fluid load
- If the SV rise increased by more than 10% after new 200ml we repeat the procedure until the SV increase is not less than 10%
- Decrease of SV for more than 10% of the value of the previous measurement requires new 200ml of fluid

-In case of hemodynamic instability or major bleeding, the bolus of fluid increases to 400 ml if the FTC below 300ms. Hemodynamic algorithm indicates the bolus administration of vasopressors and continued giving norepinephrine when mean arterial pressure falls below 70 mm Hg or giving inotropes if the cardiac index (CI) is below 2.5 L/min and stroke volume can not be increased further by giving fluids.

The measurement has been carried out until the surgery was over.

5 doses of packed red blood cells and 5 units of fresh frozen plasma were prepared for the patient. Anesthesia was maintained with sevoflurane and low-flow oxygen 1L/min. Fentanyl was given half an hour to an hour at a dose of 1mcg/kg BW.

During entire period of anesthesia, continuous monitoring of the patient was taken tracking the following parameters: blood oxygen saturation (SpO₂), expiratory CO₂ (Et CO₂), bispectral index (BIS), core temperature, invasive arterial pressure, mean arterial pressure (MAP), central venous pressure (CVP) and Cardio Q's parameters.

Phenylephrine was administered in systemic circulation or limb for prevention differential pressures between two circuits.

Using Cardio Q noninvasive monitoring we monitored cardiac output (CO), stroke volume (SV), heart rate (HR), flow time corrected (FTC), systemic vascular resistance (SVR) and oxygen delivery DO₂.

After preparing the surgical field, using extraperitoneal access, right external iliac artery and vein were mobilized, side branches clamped and after systemic administration of 300i.u./kg BW of heparin cannulation of blood vessels was performed. For cannulation we used venous cannula of 20 Fr (DLP 66120, Medtronic, Inc., Minneapolis, MN) and arterial cannula of 16Fr (DLP 66116, Medtronic, Inc., Minneapolis, MN). Esmarch tourniquet around limb proximal to cannulation site, was placed and cannulas were connected with extracorporeal circuit. Measured ACT was 490s.

Extracorporeal circulation was carried out using an integrated infant membrane oxygenator (Medtronic liliput) for its low volume prime requirement and high capacity for heat exchange, and specially adapted tubing pack (1K35R, Medtronic, Inc., Minneapolis, MN) a ¼ "tubing circuit. Y "connector is placed on the venous line to allow exsanguination in washout phase. Standard roller pump was used (HLM w/Perfusion Controller, Cobe Laboratories, Inc., Lakewood, CO) as the main console and modified perfusion heater-cooler to achieve a temperature of 42C⁰ (Hemotherm 400M, Cincinnati Sub Zero Products, Inc., Cincinnati, OH) as a heat source. Temperatures of arterial and venous blood in the limb were measured, three needle temperature probes for monitoring the temperature of the skin, muscle and tumor were placed. Temperature probe was positioned in the esophagus and the thermistor constantly controlled water temperature in the system for perfusion.

The perfusion circuit was primed with 700 ml of Ringer solution, and 2500 IU of heparin and the perfusate was warmed to 42C⁰. The values of blood flow are calculated based on the known distribution of blood for lower limb: 18% CO. Flow rate was between 400 and 800 ml/min (average flow 600 ml/min). Perfusion was started at a flow rate of 100 ml/min in order to verify that the arterial cannula is inserted correctly and that there is a good venous outflow. Flow rate was increased gradually to the pressure level in the artery that was not greater than the systemic mean arterial pressure, in order to provide a faster heating of the limb. The temperature of the limb and the tumor was maintained at 40C⁰. Patient limb was covered with a special blanket for the legs and the whole patient was heated intraoperatively with temperature of 40C⁰. The operating room was warmed up to a limit of normally tolerated temperature. The desired limb temperature was achieved after 90 minutes, and core temperature was 36,5. After reaching the desired temperature, cytostatic melphalan was given intraarterially; the dose was calculated according to formula. For the lower extremity dose was 10mg/L of limb volume ie. 100mg. Hyperthermic perfusion with melphalan had been continued for 45 minutes.

Preoperative systemic gas analyses were taken and continued during whole operation for every 30 min. Also arterial and venous gas



analyses were conducted from limb for 30 every minutes. Systemic and limb ACT were monitored for 30 minutes.

Limb washout began 45 minutes after melphalan administration at temperature of 40C⁰. It was performed by interrupting the arterial blood flow in the leg with cytostatic and redirecting the flow of venous blood towards the waste container to remove the blood. Removed blood was 2000 ml. This amount of blood has been replaced with the same amount of Ringer solution and 500 ml of Hetasorb solution and continued for their insertion in the limb artery. In this period there was a drastic drop in blood pressure, MAP, CVP, CO, SV, CI, FTC, DO₂, increased HR in the form of sinus tachycardia that went up to 130/min. Esmarch occlusion was released on the completion of the washout period. At the end of perfusion period blood vessels were closed. Protamine in a test dose of 0.5 mg was given and then was continued for administration at a dose of 0,5-1mg/100 IU of Heparin. After completion of hemostasis and drainage tube placement, operative field was closed.

The patient was transferred in the intensive care unit (ICU) until the morning for overnight continuous monitoring of vital parameters.

3. RESULTS

After the induction of anesthesia, normal hemodynamic parameters were registered.

During the period of surgical work, elevation and cannulation of blood vessels the patient was stable, fluid resuscitation was performed according to a given algorithm with 1700ml of Ringer solution.

Limb exclusion from the systemic circulation induced changes in circulating blood volume registered on Cardio Q monitor that indicated hypovolemia and peripheral vasoconstriction (table 1.). According to protocol for massive blood loss, patient got 400 ml of colloid, Hetasorb solution, and after another fluid challenge 400 ml of Ringer solution. Patient became hemodynamic stable with normovolemic values of parameters (table 2.). Phenylephrine was given to rise up MAP and to equalize it with arterial limb pressure. During heating and perfusion it was continued with application of fluid challenge according to the protocol. In those periods there were no major changes in hemodynamics and the patient was stable. In order to maintain close values of MAP and perfusion pressure, patient in 2 occasions got systemic phenylephrine. Half an hour before the start of washout period, patient received an additional 500 ml of blood due to the expected blood dilution with fluid from limb, losses from the systemic circulation that occur during flushing and because of the fall of hemoglobin in the systemic circulation up to 75g/dl. When perfusionist started with limb washout, anesthesiologist registered dramatic drop of all hemodynamic values: decrease of MAP, CVP, SV, CI, FTC and an increase in HR up to 110-130 beats/min (table 1.), which was pointing out on acute hypovolemia. Rapid fluid replacement was started giving 400 ml Hetasorb solution along with crystalloids. The patient received a total of 1200 ml of liquid. Since the patient did not immediately react to a given fluids an inotrope was included. Due to the low CO, CI and high afterload (FTC 230) we included dobutamine witch was followed by a fixing parameter values. After switching on the leg into the systemic circulation, resulting blood dilution and anemia were corrected with another 500 ml of blood and 700 ml of fresh frozen plasma (FFP).

The patient received a total of 6900ml solution and 1 L of blood, 700 ml FFP and 100ml of 8,4% Sol NaHCO₃ for metabolic acidosis correction.

During the entire operation, hour diuresis was maintained in the value of approximately 0,5-1 ml/kg BW/h, and the current period of hypovolemia did not break diuresis.

Oxygen delivery to peripheral tissue was on bottom of an acceptable range, except in those two critical moments when it was under the range and followed by increase in lactate levels up to 15 mmol/L.

The values of the monitored parameters in some critical time points are given in Table

**Tabel 1.**

Parameters	Anesth. intraduction	Before cannulation	Cannulation and Connection	Heating	Perfusion end	Washout	Protamine	Before block reversion
MAP (mmHg)	93	105	60	110	95	40	80	110
SV (ml)	64	68	41	6,0	65	33	60	90
CO (L/min)	5,2	5,9	4,14	5,4	5,3	3,6	5,4	8,5
HR (bit/min)	81	87	101	90	82	110	90	95
CI (L/min/m ²)	3,39	3,85	2,68	3,5	3,39	2,3	3,52	5,5
Ftc (ms)	363	360	320	350	370	230	330	340
DO ₂	802	702	600	780	810	540	660	650
SVR	1023	1112	1600	1300	1000	1977	1600	1200
CVP (mmHg)	6	8	3	9	7	-3	3	6
Vasopressor/ inotrop	/	/	Phenyleph.	/	Phenyleph.	Dobutamin	/	/
Fluid ammount(ml)	1700		800	3000		1200		200

MAP-mean arterial pressure; SV- stroke volume; CO- cardiac output; HR- heart rate; CI- cardiac index; Ftc- flow time corrected; DO₂- Oxygen Delivery; SVR- Systemic Vascular Ressistance

Reference values of CO (4-8 L/min), SV (60-100 ml), FTc (330-360 ms), SVR (800-1200) *, CI (2.5-4 L/min/m²), SVI (35- 65 ml/m²), DO₂ (950-1150) * According to some authors, 700-160

Tabel 2.

Parameters	Cannulation and connection	Stabilisation after cannulation	Washout	Stabilisation after washout
MAP (mmHg)	60	75	40	75
SV (ml)	41	65	33	60
CO (L/min)	4,14	5,2	3,6	5,2
HR (bit/min)	101	80	110	88



CI (L/min/m ²)	2,68	3,39	2,3	3,4
Ftc (ms)	320	340	230	335
DO ₂	466	720	600	685
SVR	1600	1000	1977	1500
CVP (mmHg)	3	5	-3	3
Fluid amount (ml)	800		1200+	Dobutamin

4. DISCUSSION

The most severe and life-threatening complications of HILP is acute hypovolemia. Communication between the systemic circulation and the isolated limb still exists although the main objective of the procedure is to separate these two circulations (11). To prevent losses on any side due to the pressure gradient between systemic and isolated limb circulation, it is necessary to maintain the equilibrium of mean arterial pressure and limb perfusion pressure (7). In the present case, there are two critical moments: the isolation of leg and washout after melphalan. It is believed that the greatest losses occur at the level of venous circulation at the washout stage (7). Low SV, CO show us a poor preload and low CI is usually result of myocardial depression. Ftc value indicating afterload and SVR can partially assess how peripheral vascular resistance is. The increase in afterload can be registered with simultaneous Ftc reduction below 330ms. This can be seen in conditions that cause vasoconstriction, e.g. hypovolemia, hypotension, hypothermia and after vasopressor application. In this case, greatest losses are due to the transition of volume of blood from the systemic circulation in the leg.

5. CONCLUSIONS

Washout period requires a good cooperation between anesthesiologist and perfusionist. It is necessary that limb washing is done gradually and to prevent rapid swelling of venous blood in the waste container. Stopping the outflow of arterial blood to the leg and redirection of venous blood in waste container result in shift of venous blood from the systemic circulation in the waste container (7). This leads to acute blood loss and sudden vasoconstriction.

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