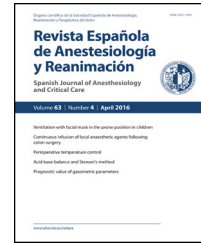




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CASE REPORT

Isolated limb perfusion with cytostatic drug leakage[☆]

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KEYWORDS

Hyperthermic chemotherapy;
Isolated perfusion;
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Abstract Isolated limb perfusion is the treatment of stage III melanoma with in-transit metastasis. This technique allows the administration of cytostatics at an effective concentration and temperature, which could not be administered systemically because of their toxicity. The toxicity due to leakage of the chemotherapy agent from the limb into the systemic circulation is the most serious short-term complication, and is manifested by a systemic inflammatory response syndrome in the immediate post-intervention period. Early detection of this complication and its peri-operative management requires a multidisciplinary approach, in which the anaesthesiologist plays a key role.

A case of isolated lower limb perfusion is reported in which the procedure had to be interrupted due to the passage of tumour necrosis factor into the systemic circulation, with severe intra-operative haemodynamic repercussions.

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PALABRAS CLAVE

Quimioterapia hipertérmica;
Perfusión aislada;
Toxicidad

Perfusión aislada de extremidad inferior con fuga de quimioterápico

Resumen La perfusión aislada de la extremidad es el tratamiento del melanoma en estadio III, con metástasis en tránsito. Esta técnica permite la administración de citostáticos a concentración y temperatura eficaces, que no podrían ser administrados de manera sistémica debido a su toxicidad. La toxicidad debido al paso a la circulación sistémica de quimioterápico procedente de la extremidad es la complicación más grave a corto plazo, y se manifiesta mediante el síndrome de respuesta inflamatoria sistémica en el postoperatorio inmediato. La detección precoz de esta complicación y su manejo perioperatorio requiere un abordaje multidisciplinar, en el que el anestesiólogo tiene un papel clave.

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Presentamos un caso de perfusión aislada de la extremidad inferior en el que el procedimiento tuvo que ser interrumpido por paso de factor de necrosis tumoral a la circulación sistémica, con grave repercusión hemodinámica intraoperatoria.

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Clinical case

We present the case of a 67-year-old woman, BMI (kg/m²) 40, with a history of arterial hypertension, diagnosed with cutaneous malignant melanoma in July 2014 following a skin lesion on the inner side of the right ankle. After a good initial response to chemotherapy (dacarbazine, ipilimumab, nivolumab), she presented new cutaneous progression in 2016, and was scheduled for inguinal and iliac lymphadenectomy plus hyperthermic isolated limb perfusion of melphalan and tumour necrosis factor (TNF) in the right lower limb (RLL).

Preoperative analytical tests were normal. The electrocardiogram (ECG) showed a sinus rhythm with ST segment depression of less than 1 millimetre in leads V5 and V6, functional capacity ≥ 4 METS, ASA: II, NYHA: II.

On the day of surgery, conventional monitoring was started, a central venous catheter was placed to measure CVP, and a PiCCO catheter was placed in the left femoral artery. Urine output and oesophageal temperature were monitored continuously, and oxygen saturation was measured at the time points established in our protocol: baseline, before starting chemotherapy infusion, at 30 min after start of infusion, after limb washout, and at the end of the intervention. Anaesthesia was induced using standard techniques and maintained with desflurane + remifentanyl. Baseline haemodynamic parameters were within normal ranges. Standard inguinal or superficial lymphadenectomy, dissection and cannulation of the femoral artery and vein were performed. Following this, a 250 mg heparin bolus was administered in order to maintain clotting time above 480 s, and a tourniquet was applied to the root of the limb. A portable gamma camera (S102 Sentinella[®], Oncovision, Valencia, Spain) was placed over the heart and 20-second interval monitoring was started. Thirty μ Ci of tracer was administered systemically, and after stabilisation 300 μ Ci was administered in the RLL. As systemic activity was stable, with a 1–2% increase, the administration of cytostatics was considered optimal.

The infusion pump was primed with blood and plasma-lyte, and the initial flow was set at 510 ml/min (the blood volume of the extremity was estimated by multiplying the weight of the patient $\times 0.15 \times 40$). The input temperature was gradually increased to 39 °C, after which continuous infusion of 1 mg melphalan was administered through the venous line of the extracorporeal circuit for 20 min, during which systemic activity gradually increased (6–8%), suggestive of leakage from the RLL. The vascular clamp was

tightened and a 4 mg bolus of TNF (tasonermin Beromun[®]) was administered via the same route. Activity increased, reaching a peak of 20%, so it was decided to discontinue infusion 17 min after starting, and limb washout was performed. Leakage from the RLL into the systemic circulation was finally quantified at 27% (Fig. 1). Total extracorporeal circulation time was 97 min. Ten minutes after starting administration of TNF, the patient presented a tendency towards hypotension, which was normalised by infusion of noradrenaline, and 20 min after suspending TNF she presented tachycardia and severe hypotension, decreased systemic vascular resistance (SVRI 580 dyn*s/cm⁵), and increased stroke volume variation (SVV 28%), with heart rate remaining at baseline levels (HR 2.5 l/min). Administration of noradrenaline was increased to 0.40 mcg/kg/min. Given the impossibility of maintaining MAP > 60 mmHg, a 2 mg/kg bolus of methylene blue was administered together with occasional boluses of epinephrine to bring volume up to 1 mg. Fig. 2 shows the intraoperative changes in haemodynamic parameters.

After performing deep lymphadenectomy, the patient was transferred to the intensive care unit under sedation and mechanical ventilation. Total intraoperative blood loss was 1000 ml. During the procedure, 1 g of Ca and 50 mEq of bicarbonate were administered to correct acid–base imbalance (Table 1).

Six hours after surgery, norepinephrine requirements progressively decreased until administration was suspended at 36 h. The patient was extubated at 24 h and discharged to the ward 4 days after the intervention. The changes in laboratory parameters during the immediate postoperative period are shown in Table 2.

Discussion

We present a case of interrupted isolated lower limb perfusion with cytostatics due to leakage into the systemic circulation, causing significant haemodynamic imbalance. The leakage of cytostatics into the systemic circulation is the most serious perioperative complication associated with this procedure.^{1,2} It is caused by the leakage of arterial or venous blood from the isolated limb into the systemic circulation. Arterial communication is due to differences between the patient's mean arterial pressure and that of the extracorporeal circuit (ECC), and can in principle be controlled by volume replacement, vasoactive drugs and/or changing ECC parameters. The administration of vasocon-

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