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Anesthetic management of carcinoid syndrome: is octreotide enough? A case report

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Abbreviations:
5-HIAA = 5-hydroxyindoleacetic acid.
ECG = Electrocardiogram.
NET = Neuroendocrine tumor.
SBP = Systolic blood pressure.

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SUMMARY

Carcinoid tumors are rare slow-growing neuroendocrine tissue neoplasms. Their ability to secrete bioactive substances to the systemic circulation is accountable for a clinical presentation known as carcinoid syndrome. Main symptoms include bronchoconstriction, flushing, diarrhea and hemodynamic instability. Octreotide, a somatostatin analogue, is the current mainstay for carcinoid syndrome treatment and perioperative management. However, no regimen has proven to be completely effective in preventing systemic manifestations and recent literature suggests that it might be an insufficient measure. We report a case of a 51-year-old male with a functioning small bowel neuroendocrine tumor and carcinoid syndrome presenting for a primary tumor resection, discussing possible pitfalls and key points in the care of these patients.

Key words: Carcinoid syndrome, neuroendrocrine tumor, anaesthetic management, hemodynamic instability, octreotide.

RESUMEN

Los tumores carcinoides son neoplasias de tejido neuroendocrino poco comunes y de crecimiento lento. Su capacidad para secretar sustancias bioactivas a la circulación sistémica es responsable por una presentación clínica conocida como síndrome carcinoide. Los principales síntomas incluyen broncoconstricción, enrojecimiento, diarrea e inestabilidad hemodinámica. Octreótido, un análogo de la somatostatina, es el pilar actual para el tratamiento del síndrome carcinoide y su manejo perioperatorio. Sin embargo, ningún tratamiento ha demostrado ser completamente eficaz para prevenir las manifestaciones sistémicas y estudios recientes indican que puede ser una medida insuficiente. Presentamos un caso de un varón de 51 años con un tumor neuroendocrino funcionante en el intestino delgado y un síndrome carcinoide, sometido a una resección del tumor primario, discutiendo posibles dificultades y puntos clave en la atención de estos pacientes.

Palabras clave: *Síndrome carcinoide, tumor neuroendocrino, manejo anestésico, inestabilidad hemodinámica, octreótido.*

BACKGROUND

Carcinoid tumors are rare slow-growing neoplasms of neuroendocrine tissues, generally originating from the gastrointestinal and bronchopulmonary systems. Their incidence is around 1/100.000 population-years[1]. Symptoms are frequently related to the secretion of bioactive substances (mostly histamine, serotonin and kinins) to

the systemic circulation, especially upon liver metastasis development. Carcinoid syndrome clinical presentation includes hypotension, hypertension, bronchoconstriction, hyperglycemia, cutaneous flushing, and diarrhea[1]. A life-threatening form of carcinoid syndrome, known as carcinoid crisis, is due to a sudden release of mediators and may be triggered by anesthesia induction or tumor manipulation[2]. The mainstay of pharmacological prophylaxis and treatment for carcinoid crisis is octreotide, a synthetic analogue of somatostatin[3]. Optimal dose and interval have not yet been established[4]. The anesthetic management of carcinoid syndrome presents several challenges, with a focus on recognizing and minimizing the increased risk of carcinoid crisis. Preventing it and providing, if needed, the appropriate treatment should also be an anesthetic goal. A high preoperative 5-hydroxyindoleacetic acid (5-HIAA) urine level and the presence of carcinoid heart disease are risk factors for a poor outcome.

CASE REPORT

A 51-year-old, 80 kg male with the diagnosis of a functioning small bowel neuroendocrine tumor (NET) was scheduled for a primary tumor resection and mesenteric lymphadenectomy. The patient had a history of labile hypertension and no anesthetic background other than an uneventful colonoscopy.

He was admitted with a three-month history of worsening epigastric pain, diarrhea, postprandial discomfort and vomiting, leading to a 34 kg weight loss. Postprandial and stress-induced cutaneous flushing were also present. At the time of surgery clinical presentation had already progressed to an intestinal subocclusion.

Preoperative evaluation revealed high serum chromogranin A levels (8.3 ng/mL), slightly elevated 5-HIAA urinary concentration (15.7 mg/24 h) and normal liver tests and serum electrolytes. Three weeks earlier a Positron-Emission Tomography Scan with Gallium68 revealed no signs of metastatic hepatic disease. Functional capacity assessment predicted a low cardiovascular risk and an electrocardiogram (ECG) showed a normal sinus rhythm. No further cardiac workup was performed.

According to hospital recommendations a 50 µg/h octreotide perfusion was started 12 hours before surgery and kept throughout the procedure.

Intraoperative monitoring included non-invasive blood pressure, pulse oximetry, 3-lead ECG, Bi-Spectral Index® and neuromuscular block quantitative monitoring. An arterial line was placed at the radial artery before induction. There was no intraoperative temperature monitoring but active warming devices were used.

The patient underwent a rapid sequence induction with Sellick maneuver. 250 µg of fentanyl, 150 mg of propofol and 80 mg of rocuronium were administered with no relevant hemodynamic changes or clinical evidence of aspiration. A nasogastric tube and urinary catheter were placed. Before starting the procedure an ultrasound guided central venous catheter was placed on the right internal jugular vein.

General anesthesia was maintained using sevoflurane in air and oxygen mixture. Boluses of fentanyl (1-2 µg/kg) and rocuronium (20 mg) were given throughout the procedure according to monitoring.

Patient's pre-induction heart rate, median arterial pressure and systolic blood pressure (SBP) were 95 bpm, 120 mmHg and 150 mmHg, respectively. Intraoperative hemodynamic goals were set at < 20% variability from basal levels. Intraoperative heart rate ranged between 69 and 94 bpm throughout the whole procedure.

Primary tumor surgical manipulation led to a significant rise in blood pressure (maximum SBP of 189 mmHg). Octreotide boluses (20-40 µg in a total of 100 µg) and a fentanyl bolus (150 µg) were given along with anesthesia deepening, without a clear response. Blood pressure control was achieved using a 50 µg/kg/min esmolol perfusion after a 40 mg bolus (Figure 1). The surgical team was notified. After the primary tumor removal blood pressure returned to its normal range and the esmolol perfusion was gradually discontinued.

Hepatic metastasis were detected intraoperatively and their resection induced an important fall in blood pressure (minimum SBP of 84 mmHg). Hypotension was successfully managed by lightening anesthesia, crystalloid administration and a gentler surgical tumor manipulation.

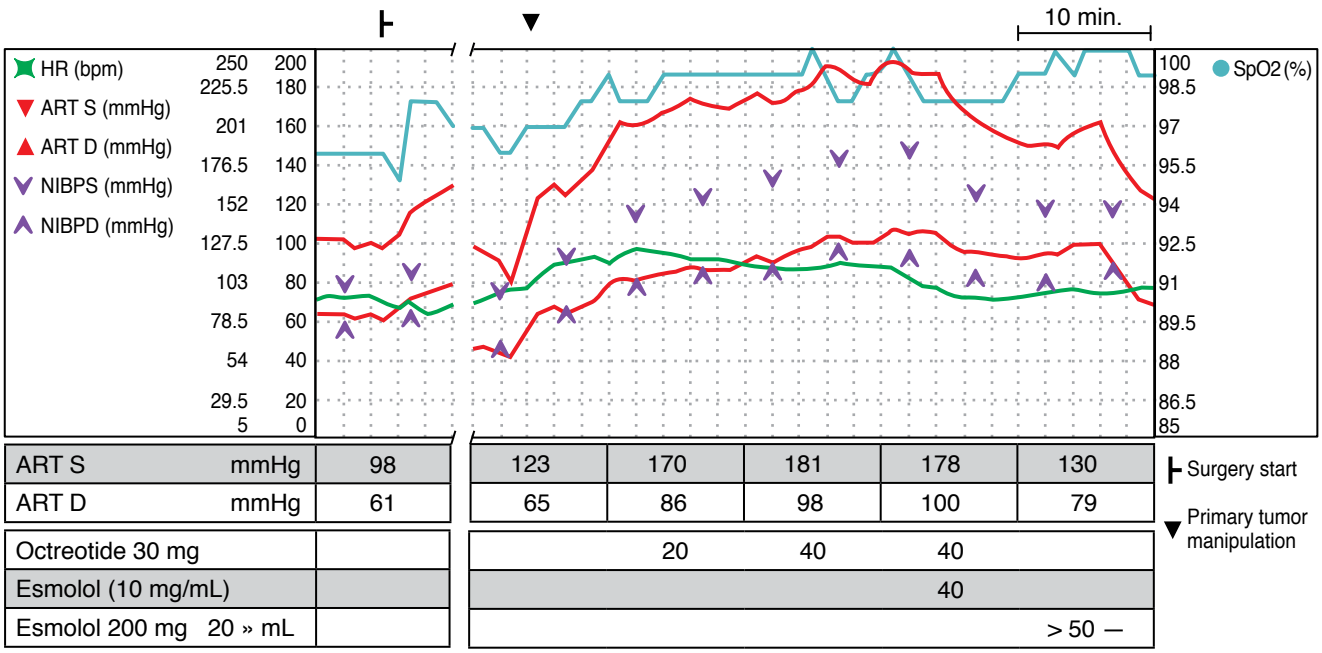
Arterial blood gas analysis throughout the procedure showed no significant disturbances, including glycemic levels. The surgical procedure lasted 2 hours 09 min without signs of flushing, bronchospasm or other complications.

Intraoperative analgesia was achieved with fentanyl boluses (total of 1 mg), paracetamol 1g and parecoxib 40 mg. The same agents were kept postoperatively together with fentanyl patient controlled analgesia.

Before arousal neuromuscular blockade was fully reversed with 400 mg of sugammadex (train-of-four 100%). Due to absent spontaneous ventilatory drive, no response to verbal and painful stimulation and modest miosis after complete sevoflurane clearance, a 0.1 mg bolus of naloxone was administered with effect.

The patient was transferred to a post-anesthetic care unit awake and hemodynamically stable. 25 mg of meperidine were administered due to intense shivering and moderate pain. No histamine release manifestations, respiratory or cardiovascular complications were registered during this period.

Immediate postoperative period was uneventful until day 17 post-surgery when he was submitted to an emergency segmental enterectomy due to anastomotic dehiscence. There



ART S	mmHg	98	123	170	181	178	130
ART D	mmHg	61	65	86	98	100	79
Octreotide 30 mg				20	40	40	
Esmolol (10 mg/mL)						40	
Esmolol 200 mg 20 » mL							> 50 —

HR = Heart rate, ART S = Invasive systolic blood pressure, ART D: Invasive dyastolic blood pressure, NIBP S = Systolic non invasive blood pressure, NIBP D = Dyastolic non invasive blood pressure, SpO2 = Pulse oxymetry.

Figure 1. Hypertension secondary to primary tumor manipulation. Blood pressure control was achieved with an esmolol perfusion.

were no signs of carcinoid crisis or cardiovascular instability during this procedure.

The patient was kept under an octreotide perfusion until the 21st day after the first surgery and it was gradually discontinued throughout four days. An echocardiogram was requested before discharge, revealing no evidence of carcinoid heart disease.

The patient was discharged at day 25 after the first intervention.

DISCUSSION

An unpredictable perioperative behavior makes NET anesthetic management challenging. Uncontrolled release of hormones can result in hemodynamic and respiratory instability, which may be unresponsive to conventional drug therapy.

Our patient presented not only with carcinoid syndrome but also with tumor growth-related complications. Diarrhea and intestinal subocclusion may result in dehydration, electrolyte disturbances or weight loss, which should be evaluated and corrected before major surgery[3].

Carcinoid heart disease is present in more than 50% of patients with carcinoid syndrome, especially those with high 5-HIAA levels and frequent episodes of flushing, although it can be underdiagnosed. Ideally, surgery should only be performed after echocardiography since symptoms do not usually develop until late stages of disease. In this case, cardiac function was not timely evaluated. In order to raise awareness and prevent error recurrence, debriefing and protocol review should be implemented.

No standard octreotide regimen has proven to be completely reliable and several recommendations have been proposed so far. According to the European guidelines for the octreotide-naive patient, a 50 µg/h perfusion was started 12 hours before surgery, supplemented with intraoperative boluses and continued over the postoperative period[3]. Considering anaesthesia duration (~3 hours) and octreotide plasma half-life (< 2 hours), a continuous infusion is likely a more effective approach than a single dose at the beginning of surgery[4].

Intraoperative monitoring is crucial to anticipate and manage carcinoid crisis and patient instability. Despite the lack of temperature monitoring, warming devices were used in order to prevent a hypothermia-triggered carcinoid crisis. Likewise, an arterial catheter was placed before potential induction-triggered hypotension. In a patient with unrecognized liver metastasis and unknown cardiac function at the time of surgery, intraoperative transesophageal echocardiography could be an excellent tool for management decisions[1]. General anesthesia without a neuraxial technique was chosen to avoid sympathetic

blockade, which would possibly require sympathomimetic drugs known to trigger the release of bioactive mediators[3]. A balanced technique was prefered because of its minimal cardiovascular effects. Sevoflurane was used over desflurane due to its better profile regarding airway resistance and sympathetic activity. Besides, there were no abnormalities in liver tests that could favour other maintenance agents. Muscle relaxation was achieved with rocuronium and analgesia with fentanyl, which are effective agents devoid of catecholamine or histamine releasing effects.

Noteworthy, this patient had both hypertensive and hypotensive episodes presumably related to surgical manipulation of the primary tumor and liver metastasis, confirming the unpredictability of carcinoid tumor behaviour despite prophylactic octreotide infusion. Hypertension required a stepwise approach including correction of reversible causes (tumor manipulation, light anesthesia and pain), octreotide boluses and beta-blocker infusion. Hypotension, the most common complication, was successfully treated with volume expansion, decreasing anesthesia depth and temporarily halting the procedure, without the need of further octreotide boluses.

Delayed emergence from anesthesia may be associated with high levels of serotonin[1], although response to naloxone suggests that opioid narcosis might also have had a role in our patient.

It is important to maintain close hemodynamic monitoring in the postoperative period, as vasoactive mediators might be secreted from residual disease[1]. Hypovolemia, pain and other sympathetic stimuli should be avoided, as should histamine-releasing opioids[3]. Accordingly, fentanyl was chosen for postoperative analgesia, however a small dose of meperidine was initially needed for shivering.

CONCLUSION

Carcinoid tumors pose special anesthetic challenges and require the intervention of a multidisciplinary team so that risks can be minimized and patient's outcomes improved. Anesthetic management begins with preoperative optimization, includes anticipation and management of hemodynamic instability during surgery, and continues throughout the postoperative period, where special attention to the analgesic approach must be given. In this regard octreotide is an important but insufficient measure. Establishing and improving an anesthetic management protocol can make the difference. Additionally, effective communication between surgeon and anesthesiologist is critical when managing intraoperative complications. Finally, given the rarity of this condition and the limited evidence available, discussion of cases and their pitfalls and, most importantly, conducting prospective research is expected to improve the management of these patients.

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