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Case Report Open Access

Carcinoid Crisis in a Patient without Previous Carcinoid Syndrome: Perioperative Management and Anesthetics Considerations - A Case Report

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Abstract

Anesthetic management of patients with carcinoid tumors can be challenging in the perioperative setting due to the risk of carcinoid mediators release which could precipitate a life-threatening carcinoid crisis. Octreotide is being used to prevent and treat carcinoid crisis, but its prophylactic scheme is not well established yet.

We report a carcinoid crisis during the anesthetic management of a 71-year-old female undergoing resection of a carcinoid tumor of the terminal ileum. This report illustrates the importance of early recognition and treatment of clinical manifestations of carcinoid crisis in order to prevent its progression.

Keywords: Carcinoid crisis; Carcinoid perioperative management

Introduction

Carcinoid tumors are slow-growing neoplasms, with an incidence reported between 0.2 and 10 per 100,000. They have origin in the cells of the neuroendocrine system and they are capable of releasing bioactive substances in the systemic circulation [1-3]. Carcinoid syndrome may occur when these substances reach systemic circulation without first being metabolized by the liver [1]. Usually, the syndrome develops from the liver metastases associated with primary carcinoids, or from primary tumors that do not drain into the portal system, bypassing hepatic metabolism [1,2]. The clinical spectrum of carcinoid syndrome includes cutaneous flushing, diarrhea, hypo or hypertension, bronchoconstriction and carcinoid heart disease [1,3]. A carcinoid crisis is a life-threatening form of carcinoid syndrome with multiple precipitants known in the perioperative period [1].

Case Report

A 71-year-old female patient appealed to the urgency service with rectal bleeding, not presenting any other complaints. She had a history of stable hypertension, diabetes mellitus type II, dyslipidemia, being under hypo coagulation medication since 1986 when she was submitted to aortic valve replacement. In the evaluation it was found anemia (hemoglobin (Hg) of 7.0 $g.dl^{-1}$)) and an international normalized ratio (INR) of 7.4, which was reverted with vitamin K; no abnormality was encountered on colonoscopy and upper gastrointestinal endoscopy. She was admitted for treatment of the anemia; 1 gram of ferrous oxide intravenous (IV) and transfusion of four units of red cells in total-and further study of the rectal bleeding. Computerized tomography showed a lesion of 1.6 cm in the distal ileum described as possibly corresponding to a neuroendocrine tumor and surrounding adenopathies with infra-pathological dimensions. Twenty-four hour urine collection revealed a raised of 5-hydroxy-indoleacetic acid of 9.5 mg day^{-1} (Normal range 1.0-7.0 day^{-1}). An octreotide-somatostatin receptor study showed a high uptake single lesion in the right flank, without metastasis. After recovering from anemia and controlling INR, the patient was discharged with small bowel resection laparotomy scheduled in 2 weeks.

Pre-anesthetic history and examination confirmed the previous findings. Other relevant information included a surgery for vein stripping, one year ago, with description of an anaphylactic reaction after the induction of the general anesthesia. Fentanyl, propofol, rocuronium and cephazolin were used previously to the event. The episode included face and thorax flushing, periorbital edema, bronchospasm and hypotension refractory to ephedrine. It was treated with intramuscular epinephrine 0.5 mg, IV fluids, hydrocortisone 200 mg IV and clemastine 2 mg IV. Tryptase elevation with maximum of 30 $\mu g.L^{-1}$ (normal range < 13.5 $\mu g.L^{-1}$) was found 3 hours after the event. Skin tests were performed but results were not available yet.

Pre-operative laboratory investigation showed an Hg of 9.4 $g.dL^{-1}$. Urea, electrolytes and chest radiograph were normal. Electrocardiogram showed sinus rhythm, complete right bundle branch block and voltage criteria of left ventricular hypertrophy. Echocardiogram showed monodisc mechanical prosthesis in aortic valve with a transprosthetic gradient of 37 mmHg, moderated mitral insufficiency, enlargement of left atrium, moderate hypertrophy of left ventricle and global systolic function preserved.

The patient was pre-medicated with metilprednisolone 125 mg the day before surgery, pantoprazole 40 mg IV in the morning of surgery and clemastine 2 mg IV and ampicillin 2 gr IV after arriving to the operating theatre. Monitoring included standard devices, invasive blood pressure, neuromuscular block (NMB) with repetitive train-of-four (TOF) stimulation of the ulnar nerve (NMT Mechanosensor®, Datex Ohmeda Division, Finland), Bispectral index (BIS) and nasopharyngeal temperature probe. Remifentanil infusion was achieved by a target-controlled infusion (TCI) system (Orchestra®,

Fresenius Vial, France). General anesthesia was induced with thiopental 300 mg and neuromuscular blockade was provided by cisatracurium 10 mg. Before endotracheal intubation lidocaine 2% 70 mg was administered. Cefoxitine 2 gr was given after endotracheal intubation. Anesthesia was maintained by sevoflurano 1-2% in air/oxygen mixture, Remifentanil TCI and cisatracurium bolus of 2 mg throughout surgery, according to the monitoring. A urinary catheter and a nasogastric tube were inserted.

Approximately 4 minutes after endotracheal intubation, it was observed flushing of face, which spread to the thorax and abdomen. Patient's blood pressure dropped and remained low despite fluid challenge and phenylephrine (total bolus of 200 µg). Simultaneously, a period of desaturation occurred, despite normal pulmonary auscultation and unchanged airways pressures. About 5 minutes after the onset of the episode, octreotide 100 µg was administered, followed by phenylephrine new bolus of 100 µg. At this moment, the arterial pressure normalized (figure 1). Tryptase was collected with maximum of 17.3 $\mu g.L^{-1}$ (normal range < 13.5 $\mu g.L^{-1}$).

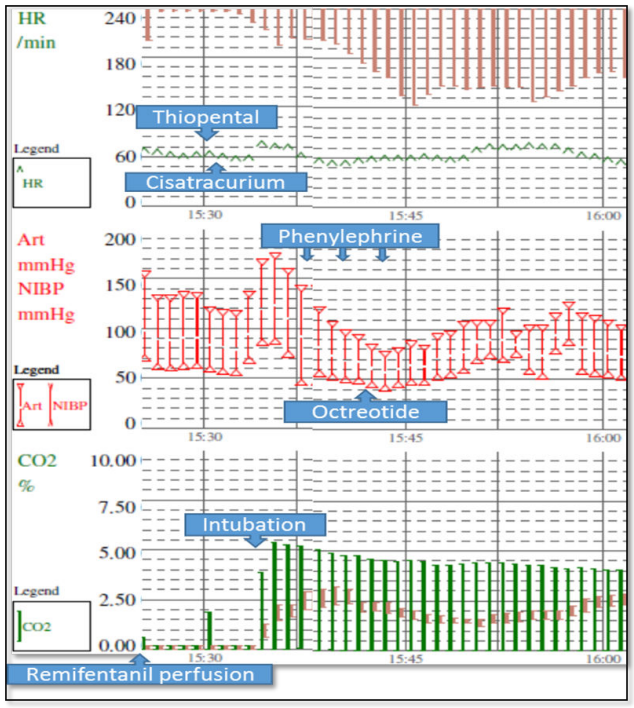

Figure 1: Clinical trends.

Additional given drugs included ranitidine 50 mg and ondansetron 4 mg. The remaining two and half hours of surgery were uneventful.

At the end of surgery analgesia was achieved with acetaminophen 1 gr, fentanyl 100 µg and infiltration of the surgical wound with ropivacaine 0.5% 20 ml. NMB was antagonized with neostigmine 2.5 mg and atropine 1 mg. Another lidocaine 2% 70 mg was administered before extubation that was carried out after consciousness and regular, spontaneous respirations resumed. The pain management in the postoperative period was achieved using a multimodal approach that included an IV Patient Controlled Analgesia (PCA) pump with morphine.

The patient remaining hospital course was uneventful and the patient was discharged on the fifth post-operatory day. Histological examination of the resected specimen confirmed the diagnosis of carcinoid tumor and the presence of nodal involvement.

Discussion

During perioperative period of a carcinoid tumor, the most important goals are to prevent the release of bioactive mediators (by avoiding triggering factors) and to perform an adequate management of an eventual carcinoid crisis (despite efforts to prevent it) [1,2]. Additionally, our patient had a previous history of anaphylactic reaction which was not fully studied. Ideally, surgery should only be performed when this study is completed, but the risk evaluation should not delay urgent or cancer surgery, like the described case [4]. In addition to the allergic reaction, we have considered the possibility of that episode being a carcinoid crisis as a first manifestation of carcinoid tumor, since many of the clinical features are shared by the two entities (hypotension, cutaneous flushing, bronchospasm, diarrhea [4-6]).

Over the last decades, several attempts have been made to prevent carcinoid crises by using certain drugs instead of others which provoke endogenous release of catecholamines and histamines [7]. Premedication with benzodiazepines and antihistamines is useful in reducing anxiety and preoperative stress [1], but its administration may be controversial, since the release of histamine occurs more often with gastric carcinoids [3]. Although steroids possibly do not avoid anaphylactic shock, they may reduce reactions caused by non-specific histamine release [4]. However, the landmark of prophylaxis involves the administration of octreotide [7] and it has been reported as an efficacious treatment of carcinoid syndrome [1] by preventing mediators release and its effects [1,3].

There are many recommendations for appropriate prophylactic use of octreotide concerning timing, duration, dose and patient selection. Some authors recommend a preoperative subcutaneous dose of 100 µg of octreotide and another 100 µg intravenously just before induction of anesthesia [3]. On the other hand, others recommend a single preoperative dose of 150-500 µg of octreotide for symptomatic patients [7]. Guidelines from the United Kingdom support prophylactic administration of somatostatin analogues to prevent a potential crisis and recommend octreotide in a constant infusion of 50 µg/hr during 12 hr before and until 14-48 hr after surgical intervention for all patients with a functioning carcinoid tumor [8]. The North American Neuroendocrine Tumor Society (NANETS) consensus guidelines recommend, in patients with suspected carcinoid syndrome who undergo major procedures, a preoperative bolus of octreotide 250-500 µg IV with extra doses available throughout the procedure [9].

However, some considerations should be done to these recommendations: firstly, they are mostly based on cases reports; secondly, all recommendations are made concerning patients with carcinoid syndrome and thirdly, outcome data of the suggested regimens' effectiveness is still not consistent. For example Kinney et al. [10] performed a retrospectively study in a group of patients who were submitted to abdominal surgery for metastatic carcinoid tumors. They found an incidence of intraoperative complication of 11% among patients who did not receive intraoperative octreotide and of 0% among those who received at least one dose. However, it is not mentioned the percentage of patients who made preoperative octreotide. Among the 6 patients who only received preoperative

octreotide alone, one (17%) had an intraoperative complication. Massimino et al. [7] evaluated retrospectively the effectiveness of 500 μg prophylactic octreotide dose on preventing carcinoid crisis in patients with carcinoid tumors (with and without carcinoid syndrome) undergoing abdominal surgeries. They found no correlations between the presence of carcinoid syndrome and intraoperative complications or carcinoid crisis; prophylactic octreotide therapy did not also show any correlation with intraoperative complications, indicating that a preoperative bolus would not prevent all intraoperative complications.

A recent meta-analysis for the prophylactic effectiveness of somatostatin analogues (SSTA) that included these two studies showed that perioperative carcinoid crisis was similar despite the prophylactic administration of SSTA, and therefore the prophylactic use of octreotide was not useful in preventing carcinoid crisis [11]. However, authors alert to the use of the results with caution, seeing that the studies included were both retrospective and that the quality of evidence is questionably. Having all of this in mind octreotide was not given prophylactically in our case, but it was available in the operation room in case it was necessary.

There are many triggers in the intraoperative setting that can stimulate the release of carcinoid mediators: the use of histamine releasing drugs, response to intubation, hypo and hypertension, insufficient analgesia and intraoperative tumor handling, among others [1].

A balanced technique is the most common an aesthetic technique reported, although combined anesthesia has been used successfully for management of patients with carcinoid tumors [1]. In our case, the patient had aortic valve prosthesis with obstruction, which is a clear contraindication to a neuraxial technique.

Considering the possibility of an allergic reaction to one of the drugs used in the previous anesthesia, we chose different drugs, as recommended in these situations [4]. The drugs were chosen taking into account their potential to release histamine and the possibility of cross-reactions. Although thiopental has a potential to release histamine, the clinical experience has not been adverse [3]. NMB agents have a high degree of cross-reactivity, 65% by skin testing [5] and, if possible, should be avoided [4,6], which was not our case. Remifentanil has a very little potential of histamine release [4] and its infusion provides adequate analgesia with suppression of the intubation stimulus and a rapid titration in order to quickly meet the analgesic requirements during the surgery.

In our case, hypotension may have several causes such as anesthetic drugs, aortic stenosis, and essential chronic hypertension and associated hemodynamic liability, release of carcinoid mediators, anaphylactic reaction and hypovolemia, among others. The hypotension should be promptly treated, because it can trigger itself the release of carcinoid mediators. However the treatment with sympathomimetic agents may even increase it [1]. Along with fluid administration, IV octreotide is the most effective treatment described for hypotension associated with carcinoid tumor [1]. In our case, by verifying the absence of response to fluid administration and phenylephrine and the onset of cutaneous flushing, we assumed facing the initial phase of a carcinoid crisis. Octreotide administration prevented its progression.

Conclusion

The use of prophylactic octreotide is widely recommended to prevent intraoperative carcinoid crisis. However, its effectiveness it is not well establish yet, neither the dose nor the duration of pre-operative octreotide.

During perioperative management of a carcinoid tumor, it is important to anticipate and prevent the release of carcinoid mediators, early recognize the clinical manifestations of carcinoid syndrome/carcinoid crisis, and to have a low threshold for treatment with octreotide when clinical manifestations appear in order to prevent its progression.

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