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Octreotide LAR and Bolus Octreotide Are Insufficient for Preventing Intraoperative Complications in Carcinoid Patients

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Background and Objectives: Surgery in carcinoid patients can provoke a carcinoid crisis, which can have serious sequelae, including death. Octreotide prophylaxis is recommended to prevent carcinoid crisis, however there are few reports of outcomes and no large series examining its efficacy. We hypothesized that a 500 μg prophylactic octreotide dose is sufficient to prevent carcinoid crisis.
Methods: Records of carcinoid patients undergoing abdominal operations during years 2007–2011 were retrospectively reviewed. Octreotide use and intraoperative and postoperative outcomes were analyzed.
Results: Ninety-seven intraabdominal operations performed by a single surgeon were reviewed. Ninety percent of patients received preoperative prophylactic octreotide. Fifty-six percent received at least one additional intraoperative dose. Twenty-three patients (24%) experienced an intraoperative complication. Intraoperative complications correlated with presence of hepatic metastases but not presence of carcinoid syndrome. Postoperative complications occurred in 60% of patients with intraoperative complications versus 31% of those with none ($P = 0.01$).
Conclusions: Significant intraoperative complications occur frequently in patients with hepatic metastases regardless of presence of carcinoid syndrome and despite octreotide LAR or single dose prophylactic octreotide. Occurrence of such events correlates strongly with postoperative complications. Randomized controlled trials are needed to determine whether the administration of prophylactic octreotide is beneficial.
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KEY WORDS: carcinoid crisis; anesthesia; neuroendocrine tumor

INTRODUCTION

Carcinoid tumors arise most commonly from neuroendocrine cells of the midgut [1]. These tumors can secrete a variety of substances including serotonin, bradykinins, tachykinins, prostaglandins, and histamine that are responsible for producing symptoms known as the carcinoid syndrome [2,3]. Carcinoid syndrome is characterized by varying degrees of flushing, diarrhea, right-sided heart failure, and bronchial constriction. Carcinoid syndrome is most commonly observed in patients with midgut primary carcinoid tumors and hepatic metastases. Normally, the liver inactivates amines and peptides released by a gastrointestinal primary tumor into the portal circulation. However, the venous drainage of hepatic metastases bypasses the portal circulation thus allowing secretion of active metabolites into the systemic circulation [2,4]. When these hormones are released into the circulation in sudden, large quantities, carcinoid crisis can occur. The much more serious entity, carcinoid crisis, has no strict definition, but is generally considered to be the sudden onset of debilitating or life-threatening features of carcinoid syndrome [5]. It is characterized by flushing, diarrhea, bronchospasm, hyperthermia, tachycardia, bradycardia, hypertension, or hypotension [6,7]. These events can have serious sequelae including complete vasomotor collapse and death. Carcinoid crises have been reported to be induced by emotional stress, pharmacologic agents, especially catecholamines, minor surgical procedures, angiography, induction of anesthesia and major operations [3,6–9]. Therefore, the possibility of provoking a carcinoid crisis should be of concern with any carcinoid patient undergoing an invasive procedure.

Over the past several decades attempts have been made to prevent crises in carcinoid patients undergoing invasive procedures by using certain pharmacologic agents and avoiding others. This strategy involves using anxiolytics and avoiding exogenous catecholamines and histamines or agents that provoke their endogenous release [2,10–13]. However, the mainstay of prophylaxis involves the administration of the somtatostatin analogue octreotide to suppress hormone release from the tumors.

Recommendations regarding appropriate prophylactic use of octreotide vary widely with respect to dose, timing, duration, and patient selection. Some authors recommend a single preoperative dose of 150–500 μg of octreotide for patients with symptomatic neuroendocrine tumors [14,15]. The North American Neuroendocrine Tumor Society guidelines recommend a bolus injection of 250–500 μg of octreotide for minor procedures. They advise having additional vials of octreotide available in the operating room or treatment area, given as repeat bolus injections of 250 μg or greater as needed. For major procedures, the authors recommend a 250–500 μg preoperative bolus and remark that continuous infusions of 50–500 μg/hr have been safely reported, but review of the references provided indicates the infusions were two single case reports [16]. All comments are made with regard to patients having carcinoid syndrome. Guidelines from the United Kingdom are more aggressive in their preoperative approach recommending constant infusion of 50 μg/hr for 12 hr before and at least 48 hr after operation for all patients with a known functioning carcinoid tumor [17]. Vaughen and Brun-

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ner addressed this subject in the International Anesthesiology Clinics. Their recommendations include octreotide 100 μg subcutaneously three times per day for 2 weeks prior to operation followed by 100 μg intravenously at the induction of anesthesia [3]. All of the guidelines recommend the use of octreotide and volume expansion for hemodynamic instability and caution that vasopressor use may increase release of serotonin and vasoactive amines from these tumors thus worsening the hemodynamic instability [2,3,15–17]. However, reports of safe intraoperative vasopressor use also exist [3].

Unfortunately, outcome data regarding efficacy of the above regimens are scant. Kinney et al. [18] attempted to address this issue when they described anesthetic use and perioperative outcome in a group of patients undergoing abdominal operations for metastatic carcinoid tumors. They found an incidence of intraoperative complication (defined as flushing, sustained hypotension, bronchospasm, and acidosis (pH < 7.2) or ventricular tachycardia) of 11% among patients who received no intraoperative octreotide and 0% among those who received at least one dose. Only six patients in their study received preoperative octreotide alone. Among these patients, one (17%) had an intraoperative complication. Therefore the incidence of carcinoid crisis among patients receiving prophylactic octreotide is unknown. Furthermore, currently published regimens emphasize use of prophylaxis in patients with carcinoid syndrome, but data on outcomes in patients with and without liver metastases or with and without syndrome are lacking.

We hypothesized that a preoperative bolus dose of octreotide would prevent carcinoid crisis and intraoperative complications in patients undergoing abdominal operations. It has been our practice to deliver a prophylactic bolus dose and have additional vials of octreotide available for administration in 250–500 μg boluses as needed for flushing, bronchospasm, changes in blood pressure, or changes in heart rate that cannot be attributed to causes other than the carcinoid tumor, such as blood loss. Initially, this was done only for patients with carcinoid syndrome. However, in recent years, our practice has been modified to deliver a prophylactic dose of 500 μg of octreotide and having additional vials available for intraoperative bolus therapy for all carcinoid patients. Herein, we report our outcomes with these practices and also attempt to determine the incidence of carcinoid crisis and intraoperative hemodynamic complications in patients with various patterns of carcinoid disease.

MATERIALS AND METHODS

Patients who underwent abdominal operations for gastrointestinal carcinoid tumors at Oregon Health & Science University from January 2007 to January 2011 were identified by review of surgical schedules. Preoperative control of carcinoid syndrome, if present, with outpatient octreotide therapy was a criterion for proceeding with operation. Information regarding patient demographics, extent of disease, presence of carcinoid heart disease, preoperative medications, operative procedure and postoperative course were obtained via electronic medical record review. Anesthesia records and operative reports were also reviewed. Anesthesia records were initially reviewed using data with vital signs recorded at 5 min intervals. If any hemodynamic events were detected at this interval, the anesthesia records were further reviewed using vital sign data recorded at 1 min intervals, so the actual duration of the event could be accurately determined. Intraoperative complications were defined as prolonged hypotension (systolic blood pressure (SBP) $\leq$80 mmHg for $\geq$10 min) or report of hemodynamic instability (including hypotension, sustained hypertension or tachycardia) not attributed to acute blood loss or other obvious causes by the attending anesthesiologist or attending surgeon. In addition, whether the attending anesthesiologist or attending surgeon declared that a carcinoid crisis had occurred in either the anesthesia record or operative report, respectively, was noted. Postoperative complications were classified into grades I–V as previously described by Dindo et al. [19] Complications of grades I and II are considered minor, generally requiring pharmacologic or bedside interventions, while grades III–V are considered major complications, generally requiring operative or radiologic interventions or resulting in death.

Univariate analyses of correlations between clinical factors and intraoperative complications were performed. Continuous variables with a Gaussian distribution were reported as means and compared with an analysis of variance. Continuous variables with a non-Gaussian distribution were reported as median and interquartile range (IQR) and compared using a Mann Whitney *U*-test. Categorical variables were compared using a χ^2 or Fisher's exact test. Multivariate logistic regression was performed using demographic variables age and gender as well as variables found to be significant on univariate analysis. $P \leq 0.05$ was considered a statistically significant result for all analyses.

RESULTS

Ninety-seven patients underwent abdominal operation by one surgeon during the study period. Table I lists demographic information for the study population. The gender distribution was roughly equal. The majority of patients had small bowel primary tumors, liver metastases, and carcinoid syndrome. The most common principal procedure performed was hepatic resection. Only 2% of patients had echocardiographic evidence of carcinoid heart disease. Ninety percent of patients received prophylactic octreotide (dose range 100–1,100 μg, median 500 μg).

Intraoperative complications occurred in 23 (24%) patients. Intraoperative complications occurred at various time points during operations. Intraoperative complications occurred at widely varied time

TABLE I. Patient Demographics and Clinical Characteristics

Characteristics	N (%)
Age (mean)	59.3
Gender	
Male	41 (42.3)
Female	56 (57.7)
ASA score	
2	24 (24.7)
3	69 (72.9)
4	2 (2.1)
Carcinoid syndrome	57 (58.8)
Carcinoid heart disease	2 (2.1)
Primary tumor location	
Small bowel	65 (67.0)
Appendix	7 (7.2)
Colon/rectum	5 (5.2)
Other	7 (7.2)
Occult	13 (13.4)
Metastases	
Hepatic	75 (77.3)
Mesenteric	46 (47.4)
Other	27 (27.8)
Principal procedure[a]	
Hepatic resection	48 (49.5)
Bowel resection	19 (19.6)
Cholecystectomy	20 (20.6)
Resection of mesenteric mass	7 (7.2)
Other	3 (3.1)

[a]Many patients had more than one procedure under the same anesthetic. The table indicates the principal procedure performed.

points during operations including anesthetic induction, incision, abdominal exploration, bowel resection, mesenteric mass resection, and liver resection. Eighteen patients (19%) experienced prolonged hypotension, as defined by our criteria in Materials and Methods Section, while 5 (5%) were reported to have marked hemodynamic instability consistent with a carcinoid crisis. Table II demonstrates the results of univariate analysis for correlations between clinical factors and intraoperative complications in our study population. By univariate analysis, complications correlated with presence of hepatic metastases, hepatic resection, placement (not use) of an epidural catheter, blood loss and transfusion. Estimated blood loss (EBL) differed between those patients with intraoperative complications and those without, with a median (IQR) EBL of 430 ml (170–1,000) and 200 ml (100–400), respectively. Four patients (17%) with intraoperative complications were transfused at least 1 U packed red blood cells (range one to six) while one patient (2.7%) without an intraoperative complication received a 1 U blood transfusion.

There were no statistically significant correlations between presence of carcinoid syndrome and intraoperative complications or carcinoid crisis. In addition, neither outpatient octreotide LAR therapy nor prophylactic octreotide therapy correlated with intraoperative complications. The dose of prophylactic octreotide among the patients who had crisis was 500 μg in three patients, while one patient each received 300 and 1,000 μg. There were statistically significant correlations between the presence of hepatic metastases or hepatic resection and intraoperative complications. While the placement of an epidural catheter correlated with subsequent hypotension, use of the epidural during operation did not. No differences in intraoperative complications were observed based on specific induction or neuromuscular blocking agents used.

In the multivariate analysis, presence of hepatic metastases was found to be a perfect predictor of intraoperative complications. Therefore, the analysis failed to converge further on any other variables so long as hepatic metastases were included in the model. However, no other variables were found to be predictive of intraoperative complications when hepatic metastases were completely removed from the multivariate model. Furthermore, subset multivariate analysis performed only among patients with hepatic metastases did not identify any other variables predictive of intraoperative complications.

Fifty-four percent of the patients who received prophylactic octreotide received at least one additional dose intraoperatively (range 100–5,500 μg; median 350 μg) and 46% of these patients had intraoperative complications. Twenty-six percent of these patients received more than one additional dose (range 2–10), including 8% who were started on an octreotide infusion. Of those who received no prophylaxis (n = 10), six patients received no intraoperative octreotide, three received intraoperative bolus doses (range one to two) and one patient was started on an octreotide infusion.

Twenty patients received no intraoperative treatment for blood pressure control. Seventeen patients (17.5%) received only additional octreotide with a median (IQR) dose of 500 μg (350–850). Twenty-three patients received only vasopressor, most commonly phenylephrine, with a median (IQR) dose of 850 μg (250–1,200). The remaining 37 patients received both octreotide and vasopressor with median (IQR) doses of 500 (450–1,000) and 800 μg (300–1,325), respectively. Twenty-four patients were treated with vasopressor infusion including 7 (30%) in the vasopressor only group and 17 (46%) in the octreotide + vasopressor group. Eight patients were treated with an octreotide infusion including 1 (6%) in the octreotide only group and 7 (19%) in the octreotide + vasopressor group.

The overall postoperative complication rate was 38%, with 21% of patients experiencing a major complication. Patients who had intraoperative complications were significantly more likely to experience increased 30-day morbidity as shown in Table III. In addition, patients with prolonged hypotension or carcinoid crisis experienced more major complications. There were two deaths (2%) in the postoperative period, one from renal failure and one from aspiration and subsequent cardiopulmonary arrest. Neither patient experienced an intraoperative complication.

TABLE II. Perioperative Characteristics of Patients With Intraoperative Complications

Characteristic	No. of pts. (total = 97)	Intraoperative complications N (%)	*P*-value
Carcinoid syndrome			0.46
Yes	57	12 (21.1)	
No	40	11 (27.5)	
Outpatient octreotide			0.75
Yes	70	16 (22.9)	
No	27	7 (25.9)	
Prophylactic octreotide			0.77
Yes	87	21 (24.1)	
No	10	2 (20.0)	
Hepatic metastases			<0.01
Yes	75	23 (30.7)	
No	22	0 (0.0)	
Hepatic resection			0.03
Yes	48	16 (33.3)	
No	49	7 (14.3)	
Epidural catheter			0.04
Yes	63	19 (30.2)	
No	34	4 (11.8)	
Epidural infusion			0.11
Yes	49	15 (30.6)	
No	48	8 (16.7)	
Induction agent			0.43
Propofol	89	21 (23.6)	
Etomidate	5	2 (40.0)	
Thiopental	3	0 (0.0)	

DISCUSSION

The overall 24% incidence of intraoperative complications in the present series was considerably higher than the previously published 7% incidence [18]. Although intraoperative complications correlated with several factors and surgical stressors on univariate analyses, multivariate analysis showed that only the presence of liver metastases was truly predictive. Intraoperative complications can occur at any time during an operation and it should be noted that neither manipulation nor resection of the liver is required for an intraoperative complication to occur. Our results might suggest that patients without hepatic metastases on preoperative imaging may not be at risk. However, in a recent publication, Chambers et al. [20]

TABLE III. Thirty-Day Postoperative Morbidity and Mortality Stratified by Intraoperative Complications in Patients Undergoing Abdominal Operations for Carcinoid Tumors

Postoperative complications	No events N (%)	Intraoperative complications N (%)	*P*-value
None[a]	51 (68.9)	9 (39.1)	0.01
Any	23 (31.1)	14 (60.9)	
Minor (grade I–II)	12 (16.2)	5 (21.7)	0.02
Major (grade III+)	11 (14.9)	9 (39.1)	

[a]Reference value for comparisons.

found that preoperative imaging failed to detect mesenteric, hepatic and peritoneal metastases in a group of patients with small bowel neuroendocrine tumors undergoing laparotomy in 16%, 14%, and 75% of cases, respectively. Therefore, all patients should be considered at risk for intraoperative complications until it is proven intraoperatively that no hepatic metastases are present.

A major new finding of this series is that intraoperative complications occurred as frequently among patients with functioning (21%) as non-functioning (28%) carcinoid tumors. At least two currently published guidelines regarding octreotide prophylaxis recommend treatment in patients with functioning neuroendocrine tumors, suggesting that patients with clinically non-functional tumors are not at risk [16,17].

Utilizing a definition of SBP $\leq$80 mmHg for at least 10 min duration, our incidence of prolonged hypotension in carcinoid patients of 19% is also considerably higher than the 7% incidence reported in adult non-cardiac surgery patients [21]. Evidence is mounting that intraoperative hypotension affects postoperative course. Reich et al. reported that post-induction hypotension was associated with prolonged postoperative stay and death [22]. Another study by Bijker et al. [23] found an increased 1-year mortality in patients with a single intraoperative systolic blood pressure of $<$80 mmHg, however this difference disappeared in the multivariate model after adjusting for other cofounders. A recently published article by Tassoudis et al. [24] found that persistent hypotension during elective major abdominal operation was a risk factor for postoperative complications and increased length of stay. Our finding that prolonged hypotension and/or notable hemodynamic instability were associated with postoperative complications strengthens the conclusions of other authors about the effect of intraoperative hypotension on postoperative course. These findings suggest that focus on preventing intraoperative hypotension in carcinoid patients may lead to decreased postoperative complications.

Previously published literature supports the notion that prophylactic octreotide is effective at preventing intraoperative complications. Some sources list the effectiveness of prophylactic octreotide as nearly 100% [14]. In our series, outpatient therapy with octreotide did not prevent all intraoperative complications. Single dose prophylactic octreotide was clearly not 100% effective. Based on our results, we conclude that neither outpatient octreotide LAR nor single dose preoperative bolus octreotide prevent all intraoperative complications.

Kinney et al. [18] reported that intraoperative doses of octreotide prevented intraoperative complications (including prolonged hypotension) in all of their patients who received one, implying that it is virtually100% effective. However, it is not clear from their report why or when patients were administered intraoperative octreotide. In the present series, 54% of patients received intraoperative octreotide, 26% of whom received multiple doses. Despite these intraoperative doses, 46% of patients had additional intraoperative complications. Therefore, our results do not support the concept that intraoperative octreotide is virtually 100% effective at preventing intraoperative complications.

Seventy-nine percent of patients were given some intraoperative treatment for blood pressure control. More patients were given additional boluses octreotide (with or without vasopressors) than vasopressors alone. However, the administration of additional doses of octreotide was not associated with improved patient outcomes either intraoperatively or postoperatively. This is consistent with previously published literature [18]. Our results also suggest that intraoperative use of the vasopressor phenylephrine in carcinoid patients is safe.

Based on the results of the present series, we conclude that significant intraoperative complications occur more frequently among carcinoid patients undergoing abdominal operations than previously reported. The risk appears to be confined to patients with hepatic metastases, but, notably, was observed in patients regardless of whether or not they had clinical carcinoid syndrome. Because a significant percentage of patients have hepatic metastases found only at operation, we conclude that surgeons and anesthesiologists should consider all carcinoid patients to be at risk. The occurrence of intraoperative complications correlated strongly with postoperative complications. However, octreotide therapy, regardless of whether it was given on an outpatient basis, as a preoperative bolus, or an intraoperative bolus, neither prevented all nor substantially reduced the incidence of intraoperative complications.

Currently, it is not known whether continuous octreotide infusions would be more effective at preventing intraoperative complications or whether such prevention would reduce postoperative complications. Future studies should systematically address the impact of specific octreotide infusion regimens on both intraoperative and postoperative outcomes. In the meantime, surgeons and anesthesiologists should always be prepared to aggressively treat intraoperative hemodynamic instability with additional octreotide, intravenous fluids, and vasopressors.

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