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B-Adrenergic agonist administration is not associated with secondary carcinoid crisis in patients with carcinoid tumor

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ABSTRACT

Background: Patients with carcinoid tumors are at risk for profound intraoperative hypotension known as carcinoid crisis, which catecholamines are traditionally believed to trigger. However, data supporting this are lacking.
Methods: Anesthesia records were retrospectively reviewed for carcinoid patients treated with vasopressors. Hemodynamics for those with crisis were compared between those who received β-adrenergic agonists (B-AA) versus those who did not.
Results: Among 293 consecutive operations, 58 were marked by 161 crises. There was no significant difference in the incidence of paradoxical hypotension with B-AA compared to non-B-AA ($p = 0.242$). The maximum percent decrease in mean arterial pressure following drug administration was significantly greater in those patients treated with non-B-AA than with B-AA (31.6% vs. 12.5%, $p < 0.0001$). There were no differences in crisis duration ($p = 0.257$) or postoperative complication rate ($p = 0.896$).
Conclusions: β-Adrenergic agonist use was not associated with paradoxical hypotension, prolonged carcinoid crisis, or postoperative complications in patients with intraoperative carcinoid crisis.

Background

Carcinoid tumors are rare neuroendocrine neoplasms with an incidence of approximately 2.5–5.0 per 100,000 persons per year in the United States.[1] They can arise from a variety of locations within the gastrointestinal tract, bronchopulmonary system, and urogenital system, although the most common origin is the small bowel.[2] These tumors present a particular challenge during general anesthesia because there is a risk of intraoperative carcinoid crisis with any intervention.[3–6] Carcinoid crisis is a life-threatening feature of carcinoid disease characterized by the abrupt onset of marked hemodynamic instability. It is also sometimes accompanied by flushing and bronchospasm.[7,8] While no consensus has been reached in the literature regarding a specific definition for carcinoid crisis, Kinney et al., in 2001 used the criterion of a systolic blood pressure (SBP) of less than 80 mmHg for at least 10 min, while also observing for flushing, bronchospasm, arterial pH < 7.2, and tachycardia >120 beats per minute.[7] However, subsequent studies have since shown an increased risk of major postoperative complications with a crisis duration of 10 min or greater,[9] making it unethical to withhold treatment in the interest of declaring a hypotensive event a carcinoid crisis by requiring it to last greater than 10 min. Thus, a working definition of an episode of hemodynamic instability with an SBP of <80 mmHg or >180 mmHg, not attributable to other etiology such as compression of the vena cava, has been used as an alternative.[5] Under this definition, carcinoid crisis has been described in a wide range of patients with carcinoid disease and has been reported to occur in up to 30% of operations in this population, with hepatic metastases, longer anesthesia times, and carcinoid syndrome identified as significant risk factors.[5]

Despite the high risk of prolonged hypotension inherent to carcinoid crisis, determination of an effective regimen for pharmacologic treatment has proven difficult. The exact pathophysiology of carcinoid crisis is not well understood, and it has generally been attributed to a massive release of the vasoactive hormones known to be secreted by carcinoid tumors, including serotonin,

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histamine, and bradykinin.[1] The postulated involvement of bradykinin in particular, which is thought to be responsible for the flushing in carcinoid syndrome,[10] has raised concerns that anesthetic management utilizing β-adrenergic agonists could trigger paradoxical hypotension severe enough to be a secondary carcinoid crisis.[8,11,12] While few studies have examined this question specifically, one performed by Mason et al., in 1966 observed the vascular response in the forearm to systemic epinephrine injection in 7 carcinoid patients. The authors noted decreased systemic blood pressure, decreased vascular resistance, and an elevated bradykinin level for 5 min after injection, although the response was quite variable between the 7 patients and the changes in blood pressure would not have constituted a carcinoid crisis by the modern definition described above.[13] Epinephrine has also been shown to induce flushing in patients with carcinoid syndrome.[14] Outside of such carcinoid syndrome studies, however, data supporting the widespread concern over use of β-adrenergic agonists remain very limited. It is unclear if the effects of epinephrine injection detailed above have a clinical significance in the context of intraoperative carcinoid crisis, particularly as use of β-adrenergic agonists has been reported in tertiary centers when the traditionally used agents, namely phenylephrine and vasopressin, proved insufficient.[7]

Given the paucity of data to support the continued avoidance of β-adrenergic agonists despite few other options being available for treating carcinoid crisis and the high risk associated with prolonged hypotension, this study seeks to determine whether β-adrenergic agonists such as ephedrine, norepinephrine, and epinephrine are associated with provocation of a secondary carcinoid crisis. Secondary outcomes include comparison of the duration of hypotension associated with carcinoid crisis and the rate of postoperative complications.

Methods

This study was reviewed and approved by the Oregon Health & Science University Institutional Review Board (IRB), and review of the medical record was exempted from informed consent by the IRB. All data collection and storage was compliant with the Health Insurance Portability and Accountability Act of 1996.

Patients with carcinoid tumors who underwent consecutive elective abdominal operations from 2011 to 2017 were identified by review of surgery schedules, and those who were treated with vasopressors for intraoperative hypotension and had at least one carcinoid crisis declared were included. Consensus of the operating surgeon and the attending anesthesiologist was necessary to declare a hypotensive event a crisis. All operations were performed by the principal investigator (RFP). Information regarding patient demographics and operative course was obtained from the electronic medical record. The electronic anesthesia record provided vital sign and drug administration data as well as details of the anesthetic course with 1 min time-stamped resolution. During the study period, the institutional protocol for perioperative octreotide prophylaxis of carcinoid crisis was administration of a 500 μg pre-operative bolus of intravenous octreotide followed by an intravenous infusion at a rate of 500 μg per hour for the duration of the operation. This protocol was developed for previous publications investigating whether continuous infusion of octreotide prevented carcinoid crisis. A secondary carcinoid crisis was defined as paradoxical hypotension consisting of a mean arterial pressure (MAP) drop of ≥20% at any point in the 15 min following drug administration. This definition was intentionally broad to ensure capture of all potential events. MAP recovery was defined as a return of the MAP to the last value recorded prior to drug administration. Medication doses were determined by anesthesia staff on an individual basis in response to the patient's clinical course. Adjustments to continuous infusions were not considered separate drug administrations.

Comparisons of patient characteristics, operative course, and hemodynamic changes were performed using χ^2 analysis, independent sample t-tests, and Fisher's exact test. IBM SPSS Statistics for windows, Version 24.0, Armonk, NY was used for all statistical analyses. Dose-response curves were generated by plotting each bolus dose of the medications studied as the independent variable versus the associated percent decrease in MAP in the 15 min following drug administration as the dependent variable. Continuous infusions were not included. The best fit relationship was determined for each. Dose-response curves were created using Microsoft Excel Version 14.0, 2010. The level of significance was set at $p \leq 0.05$.

Results

Two hundred ninety three consecutive elective abdominal operations between 2011 and 2017 were reviewed. Fifty eight operations on 56 patients were identified in which the patient had at least one carcinoid crisis and during which vasopressors were used for treatment of intraoperative hypotension. All patients included in this study followed the established octreotide protocol with the exception of one patient for whom a preoperative dose was not documented but who did receive a continuous infusion intraoperatively. Forty eight patients (83.9%) had carcinoid syndrome. Forty nine patients (87.5%) had hepatic metastases and 43 (76.7%) had mesenteric metastases. The most frequently performed operative procedures were hepatic debulking (63.8%), resection of a primary tumor (56.9%), prophylactic cholecystectomy (44.8%), and resection of a mesenteric nodal mass (43.1%). The majority (72.4%) of operations included a combination of operative procedures. Three (5.2%) operations were aborted due to severe carcinoid crisis. Mean duration of anesthesia was 375 min (50–753 min) and mean estimated blood loss (EBL) was 853 mL (0–6000 mL). Median hospital length of stay was 8 days (0–53 days). There were 161 carcinoid crises declared during these operations with a mean duration of 9.1 min (2–58 min).

The included patients received a total of 547 doses of phenylephrine (of which 209 were given specifically to treat a carcinoid crisis, 38.2%), 195 doses of vasopressin (51.3% of which for crisis), 43 doses of ephedrine (41.9% of which for crisis), 16 doses of norepinephrine (37.5% of which for crisis), and 29 doses of epinephrine (93.1% of which for crisis). Ephedrine, norepinephrine, epinephrine, or a combination of these β-adrenergic agonists was administered in 22 operations (37.9%). Phenylephrine or vasopressin was attempted prior to use of a β-adrenergic agonist in all but two operations. There were no significant differences between those who received a β-adrenergic agonist and those who did not in any of the demographic or operative variables examined, including age, gender, duration of anesthesia or estimated blood loss (Table 1).

Regarding carcinoid crisis, there was no significant difference in the duration of carcinoid crisis between those treated with phenylephrine/vasopressin only and those treated with a β-adrenergic agonist (8.08 vs. 10.73 min, $p = 0.257$). Similarly, there were no significant differences in the lowest recorded systolic blood pressure (64.3 vs. 62.2 mmHg, $p = 0.583$), duration of systolic blood pressure less than 80 mmHg (11.4 vs. 13.8 min, $p = 0.553$), or duration of tachycardia greater than 120 beats per minute (0.72 vs. 3.0 min, $p = 0.439$). There was no difference in the rate of 30-day postoperative complications between those

Table 1
Comparison of demographic and operative variables for patients with carcinoid disease, grouped by treatments for intraoperative hypotension.

	Phenylephrine/vasopressin only (N = 36)	β-adrenergic agonist (N = 22)	*p*-value
	N (%) or Mean (SD)	N (%) or Mean (SD)	
Age (years)	60.64 (9.5)	62.00 (7.6)	0.572
Female sex	24 (66.7)	16 (72.7)	0.628
Small bowel primary tumor	33 (94.3)	20 (90.9)	0.627
Hepatic metastases	32 (88.9)	19 (86.4)	0.775
Mesenteric metastases	27 (75)	18 (81.8)	0.545
Other metastases	11 (30.6)	10 (45.5)	0.252
Carcinoid syndrome	30 (83.3)	19 (86.4)	0.757
Length of stay (days)	11.25 (10.2)	10.45 (8.4)	0.795
Duration of anesthesia (minutes)	371.08 (132.2)	382.55 (148.2)	0.761
Volume of crystalloid administered (mL)	4125.92 (2034.9)	4602.95 (3207.8)	0.490
EBL (mL)	769.7 (706.0)	988.4 (1430.6)	0.440
Units packed red blood cells administered	0.69 (1.7)	1.32 (3.0)	0.314

Note. SD = standard deviation, EBL = estimated blood loss. *P*-values reported from χ^2 analysis and independent sample t-tests. $P \leq 0.05$ considered significant.

who received a β-adrenergic agonist and those who did not (54.5% vs. 52.7%, p = 0.896), nor were there differences in the rate of Clavien-Dindo Class I-II complications (36.4% vs. 38.9%, p = 0.847) or Clavien-Dindo Class III-V complications (18.2% vs. 13.9%, p = 0.661).[15] There was one mortality, which occurred in a patient who had received a β-adrenergic agonist intraoperatively. The cause of death was postoperative hepatic failure from thrombosis of the left hepatic artery following right hepatectomy, which subsequently resulted in multiple organ dysfunction and transition to comfort care measures on postoperative day 9.

Comparison of the rate of possible secondary carcinoid crisis revealed no significant difference between operations in which phenylephrine and/or vasopressin only were administered and operations in which β-adrenergic agonists were administered (20.7% vs. 12.9%, p = 0.242). The maximum percent decrease in MAP within 15 min of drug administration was significantly greater for phenylephrine and vasopressin than for β-adrenergic agonists (31.6% vs. 12.5%, p < 0.0001), but there was no significant difference in mean percent MAP decrease between these two groups (9.5% vs 6.3%, p = 0.118). There were no significant differences between the two groups in the maximum time to MAP recovery (9.0 vs. 9.8 min, p = 0.815) or in the mean time to MAP recovery (6.8 vs. 12.7 min, p = 0.277) (Table 2).

Dose-response curves were generated for phenylephrine, vasopressin, ephedrine, and epinephrine, and the best fit was found to be linear for each agent. The curves generated revealed no significant linear association in the percent decrease in MAP with increasing doses of ephedrine or epinephrine ($R^2 = 0.003$, p = 0.780, and $R^2 = 0.006$, p = 0.661, respectively). These findings were similar to phenylephrine and vasopressin, which also showed no significant association ($R^2 = 0.001$, 0.724, and $R^2 = 0.001$, p = 0.767, respectively).

Discussion

This study examined the use of vasoactive medications in patients with intraoperative carcinoid crisis to determine whether an association between provocation of a secondary carcinoid crisis and β-adrenergic agonist administration could be detected. If so, it would justify avoiding these medications in the face of a clinical indication for their administration. However, this was not observed.

There was no significant difference in the magnitude of MAP decrease in the 15 min following β-adrenergic agonist administration when compared with the 15 min following phenylephrine or vasopressin administration. Additionally, the duration of carcinoid crisis was not increased with administration of β-adrenergic agonists. While it may be argued that crisis duration is likely determined by a variety of factors, β-adrenergic agonists were generally given only after treatment had been attempted with either phenylephrine or vasopressin. Thus, the similarity in crisis duration between patients who had received a β-adrenergic agonist and those that had not may actually reflect successful treatment with β-adrenergic agonists of more refractory hypotensive episodes. Regardless, these findings suggest that there is no increased risk of vasopressor induced crisis with intraoperative use of β-adrenergic agonists in carcinoid patients over the use of phenylephrine and/or vasopressin alone.

Given that the data in this study come from retrospective review of the intraoperative management of unstable patients who were receiving multiple simultaneous treatment modalities, the authors

Table 2
Comparison of carcinoid crisis characteristics and changes in blood pressure associated with vasopressor administration, grouped by treatments of intraoperative hypotension.

	Phenylephrine and/or vasopressin only (N = 36)		B-adrenergic agonist (N = 22)		*p*-value
	N (%)	Mean (SD)	N (%)	Mean (SD)	
Duration of carcinoid crisis (mins)		8.08 (5.5)		10.7 (12.0)	0.257
Lowest recorded SBP (mmHg)		64.3 (10.9)		62.2 (14.9)	0.583
Duration of SBP < 80 mmHg (mins)		11.4 (13.3)		13.8 (17.2)	0.553
Duration of HR > 120 bpm (mins)		0.72 (2.6)		3.00 (13.4)	0.439
All postoperative complications	19 (52.7)		12 (54.5)		0.896
Clavien-Dindo Class I-II	14 (38.9)		8 (36.4)		0.847
Clavien-Dindo Class III-V	5 (13.9)		4 (18.2)		0.661
Rate of paradoxical hypotensive events (%)		20.7 (20.8)		12.9 (29.2)	0.242
Maximum MAP decrease within 15 min of drug administration (%)		31.6 (13.5)		12.5 (12.7)	<0.001*
Mean MAP decrease within 15 min of drug administration (%)		9.5 (7.0)		6.3 (7.9)	0.118
Maximum time to MAP recovery (mins)		9.0 (7.8)		9.8 (10.4)	0.815
Mean time to MAP recovery (mins)		6.8 (4.6)		12.7 (12.9)	0.277

Note. SD = standard deviation, SBP = systolic blood pressure, HR = heart rate, bpm = beats per minute, MAP = mean arterial pressure. Paradoxical hypotensive event rate was defined as a decrease in MAP ≥20% within 15 min of drug administration. Time to MAP recovery was defined as the number of minutes between the lowest MAP that occurred in the 15 min following drug administration to its return to its pre-drug administration level. *P*-values reported from χ^2 analysis and independent sample t-tests. *$P \leq 0.05$ considered significant.

caution against broadly concluding that epinephrine, norepinephrine, or ephedrine are equivalent in safety or efficacy to phenylephrine or vasopressin in this patient population. This study is also limited by its retrospective nature, small sample size, and single institution design. Based on these findings, though, it is recommended that β-adrenergic agonists be considered to treat refractory hypotension in carcinoid patients if phenylephrine and vasopressin prove insufficient (Fig. 1).

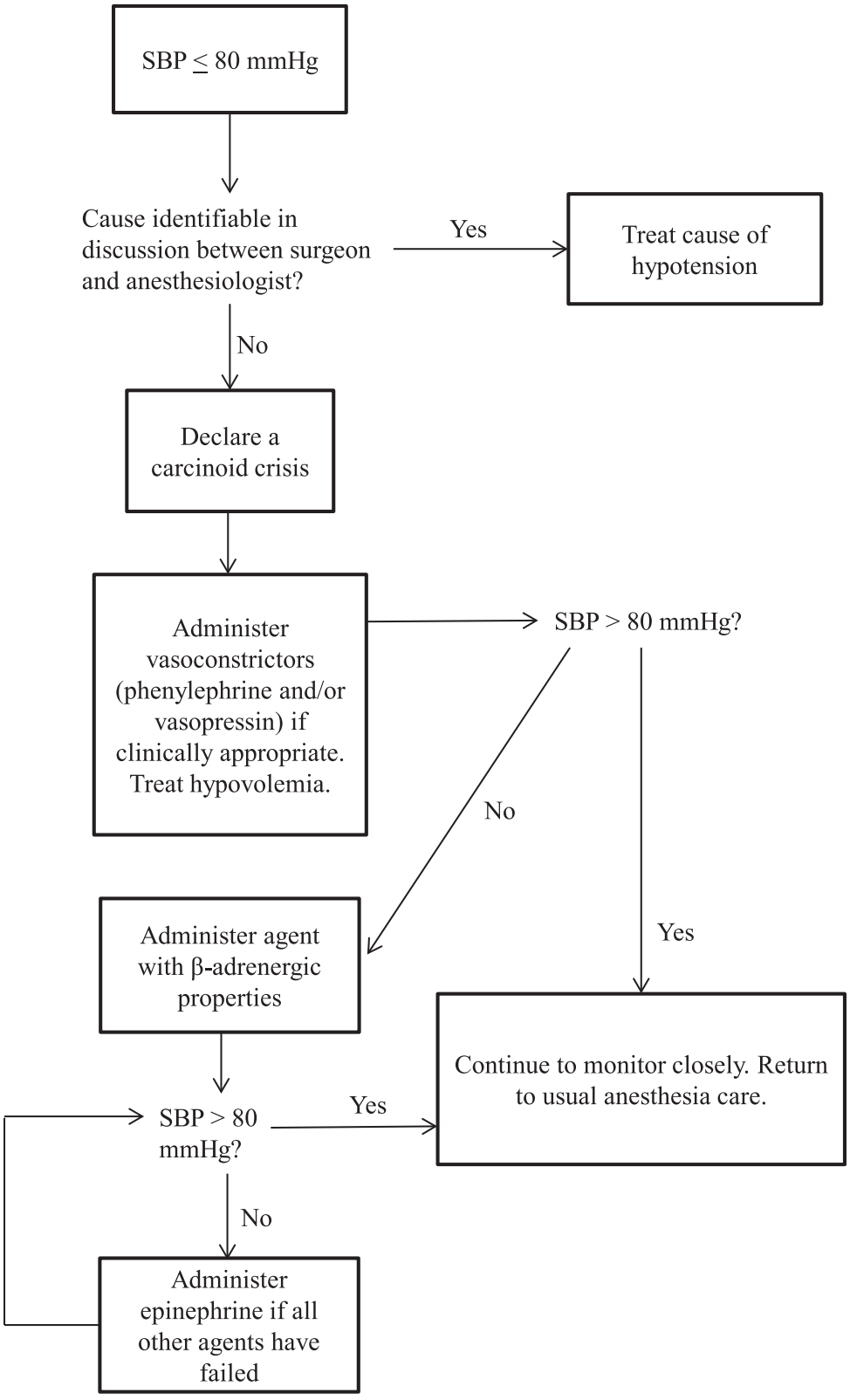

Fig. 1. Flow chart of approach to treatment of intraoperative hypotension in patients with carcinoid tumors.

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