Perioperative Management of Carcinoid Syndrome-An Anaesthesiologist’s Perspective

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Abstract

Occurrence of carcinoid syndrome is very rare. So the expertise and literature on this syndrome is limited. Physiologically active substances that are secreted by the carcinoid tumour cause major problems for the anaesthesiologist in the perioperative period. Preoperative preparation of the patient is the most important step that decides the recovery of the patient. Discovery of octreotide lead to the improvement in treating and decreasing the morbidity and mortality during surgery. If the surgery is palliative post-operative management also makes it difficult for the anaesthesiologist. Extreme vigilance and common sense had to be applied during the surgery by the anaesthesiologist. Pathophysiology, symptomatology, diagnosis and perioperative management are described in this article.

Keywords: Carcinoid syndrome; Octreotide; Serotonin; Anaesthesia

Pathophysiology

Carcinoid syndrome is caused by the action of the physiologically active substances secreted by the carcinoid tumor. Depending on the site of origin they secrete a variety of physiological substances. They are serotonin, histamine, bradykinin, insulin, glucagon, catecholamine, kallikrein, prostaglandins, substance-P, dopamine, neuropeptide-K, gastrin, tachykinins, etc. They produce a variety of symptoms and signs (Table 1). Midgut tumors commonly cause symptoms; foregut tumors cause moderate symptoms and hindgut tumors rarely produce symptoms. Serotonin is the commonest substance produced by the carcinoid tumor. Histamine is usually secreted by the gastric carcinoids [7]. Serotonin is produced by hydroxylation and decarboxylation from an essential amino acid tryptophan. Oxidation and dehydrogenation metabolize it to 5-hydroxyl indole acetic acid (5-HIAA) to be excreted in urine. As tryptophan is an essential amino acid, hypersecretion of the serotonin by the carcinoid tumor may lead to hypoproteinemia leading to pellagra-like effects. If diarrhea occurs, it leads to loss of water, sodium, chloride and potassium from small intestine leading to further electrolyte imbalance. Sympathetic stimulation commonly produces kinins. Bradykinin and tachykinin are the Kinins that are often produced. Bradykinin is broken down by plasma aminopeptidases and kininases.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Signs and symptoms</th>
<th>Causative Physiologically active substances</th>
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<tbody>
<tr>
<td>1</td>
<td>Diarrhea</td>
<td>Serotonin and prostaglandin E&amp;F</td>
</tr>
<tr>
<td>2</td>
<td>Bronchoconstriction</td>
<td>Serotonin, bradykinin and substance-P</td>
</tr>
<tr>
<td>3</td>
<td>Hypotension</td>
<td>Histamine, bradykinin</td>
</tr>
<tr>
<td>4</td>
<td>Hypertension</td>
<td>Serotonin</td>
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Diagnosis can be diagnosed by CT scan, MRI scan or PET scan [3]. Functional substances majority of the symptoms occur due to the failure of the extent of the disease.

Table 1: Physiological substances that are secreted by carcinoid tumors and their common effects.

<table>
<thead>
<tr>
<th></th>
<th>Signs and Symptoms</th>
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<tbody>
<tr>
<td>5</td>
<td>Episodic cutaneous flushing</td>
<td>Kinins and histamine</td>
</tr>
<tr>
<td>6</td>
<td>Long term Cardiac effects</td>
<td>Tachykinins</td>
</tr>
<tr>
<td>7</td>
<td>Positive chronotropic and ionotropic effects on the heart</td>
<td>Serotonin</td>
</tr>
<tr>
<td>8</td>
<td>Prolonged drowsiness after anaesthesia</td>
<td>Serotonin</td>
</tr>
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Signs and Symptoms

The physiologically active substances produce signs and symptoms which cause problems during anesthesia. The commonest sign is flushing (94%), which is the most warning sign of other signs and symptoms [8]. The triggering factor might be food such as banana, eggplant, walnuts, tomatoes, plums, etc. [9]. Flushing may be followed by dizziness, diarrhea, wheeze and electrolyte abnormalities.

Asthma can occur in 19% of patients [8]. Cardiac symptoms can occur due to the fibrosis of the pulmonary and tricuspid valves caused by the secretions leading to regurgitation and stenosis, which finally can result in cardiac failure [10]. As the lung can neutralize the substances majority of the symptoms occur due to the failure of the right heart. If the secretions cross the lung, then only left side symptoms to appear. Hyperglycemia can also occur as serotonin stimulates glycogenolysis.

Carcinoid crisis may occur, in which profound bronchospasm, hypo/hypertension, flushing and circulatory collapse may occur. Surgical preparation consists of titrating adrenergic, histaminergic & serotonin receptor blocking drugs to maximum effect while monitoring intravascular volume status & adding somatostatin before surgery. Somatostatin & its analog octreotide is the primary drug that is used in preparation. It inhibits the exocrine and endocrine secretions from gut thereby controlling signs and symptoms of Carcinoid tumor and preventing Carcinoid crisis [14,15]. The half-life of somatostatin is 1 to 3 min, and that of octreotide is 1.5 to 3 hrs. So it requires a subcutaneous injection or intravenous infusion to maintain the antagonistic effects. Various regimens and doses are proposed to decrease the signs and symptoms to the maximum effect. The commonly used regimen is starting octreotide 50 to 200 µg subcutaneously three times a day two weeks before the surgery and 100 µg again just before the induction of anesthesia to prevent the release of secretions [16,17]. We can start octreotide 24 hrs before surgery in semi-emergency situations. If the symptoms subside after the surgery octreotide has to be discontinued slowly over a period of a week [16].

Effects of histamine can be countered by antihistaminic such as chlorpheniramine for flushing and H2 receptor antagonists for gastric symptoms [8]. Carcinoid suppressor therapy can counter bronchospasm. But if the symptoms persist then steroid and anticholinergic nebulization can be done. B-Adrenergic agonists should be used cautiously as these can stimulate adrenergic system leading to carcinoid crisis.

Diarrhea can be treated symptomatically, and the electrolyte imbalance should be corrected. If needed loperamide can be used. Aprotinin is used to block kallikrein effects. It also inhibits platelet aggregation & intrinsic coagulation. So monitor coagulation profile [8].

Premedication

Premedication has to be given to avoid stimulation of the carcinoid crisis and to relieve already present symptoms [18]. Anxiety is one of the triggering factors which cause the occurrence of carcinoid crisis. So to prevent anxiety, anxiolytics like benzodiazepines have to be given [8]. To prevent bronchospasm and to combat histamine effects, an antihistaminic such as chlorpheniramine can be administered. If the patient is asymptomatic and has only carcinoid tumor but not carcinoid syndrome role of octreotide is controversial. But if the patient is a known case of carcinoid syndrome one of the recommended regimens of octreotide had to be followed (as given above). At the same time, octreotide had to be kept in the operation theater loaded at a concentration of 10 µg/ml to tide over any crisis. There are many agents in the literature that are advised to be given as premedication, but their role is not yet proved or controversial (methysergide, ketanserin, cyproheptadine, steroids,

Preoperative assessment

History and physical examination have to be done to assess the severity of the symptoms and signs. Type of test that had to be done depends on the gravity and extent of the disease. Apart from routine investigations such as complete hemogram, blood glucose levels, serum electrolyte levels, ECG, chest X – ray, the other studies that are to be done depends on the severity of the disease and the site of surgery. The tests that are commonly done are echocardiography, liver function tests, renal function tests and other imaging studies to know the extent of the disease.

Preoperative preparation of the patient

Surgical preparation of patient with Carcinoid syndrome is difficult like that of pheochromocytoma. If the patient is not prepared properly
diphenhydramine) [19,20]. They supposedly inhibit the actions of various substances that are secreted by the carcinoid tumor.

**Goals of Anesthesia**

- Prepare the patient properly so that the majority of the receptors of serotonin and other physiologically active substances are blocked preoperatively.
- Don’t use drugs or procedures that can stimulate the release of physiologically active substances.
- Treat the effects of the physiologically active substances timely or anticipate and prevent their effects intraoperatively.
- Avoid hypoxia, hypothermia, hyperventilation to prevent delayed recovery.

**General anesthesia**

**Induction**

All the commonly used induction drugs were tried in the literature. But the most widely accepted induction drugs are propofol and etomidate. As thiopentone can cause histamine release due the presence of Sulphur atom, preferably it should be avoided. Propofol can prevent the intubation response better than the etomidate, but etomidate gives excellent cardiovascular stability than propofol. So the use of etomidate with another good drug to prevent intubation response is the ideal choice for induction and propofol is an acceptable alternative [2].

**Intubation**

Use of suxamethonium is controversial in carcinoid syndrome or tumor as it causes muscular fasciculations which can cause the release of physiologically active substances into the blood [21-23]. But some reports in the literature suggest the use of suxamethonium without any complications [24]. So to prevent controversy it is always better to use a non-depolarizing neuromuscular agent for intubation if the anesthesiologist didn’t suspect any difficult intubation.

**Maintenance**

Maintenance is commonly done by intermittent positive pressure ventilation+O2+a opioid+inhalational agent+non-depolarizing neuromuscular blocking agent. Nitrous oxide can be used as it doesn’t cause any harmful effects in this surgery. An opioid that doesn’t cause release of histamine should be employed. Commonly used opioid is fentanyl, as it gives excellent cardiovascular stability and has less potential for histamine release. Vecuronium is the non-depolarizing neuromuscular blocking agent of choice as it offers excellent cardiovascular stability and has less potential for histamine release at the same time it doesn’t cause sympathetic system stimulation. Rocuronium is the alternative drug which was proposed for the vecuronium [8]. Any inhalational agent which has the property of low blood gas solubility should be used as serotonin causes delayed awakening from anesthesia. So desflurane can be preferred. But isoflurane has excellent cardiovascular stability, so the majority of the reports support it. But it is better to use more opioid-based anesthesia than the inhalational based anesthesia, as inhalational agents cause myocardial depression and lead to cardiovascular instability and release of substances [8].

**Monitoring and equipment**

Intraoperative monitoring depends on the severity of the preoperative condition of the patient. As the patient can develop exaggerated cardiovascular responses during induction also, an invasive arterial line has to be secured before induction of the patient. Monitoring of the central venous pressure (CVP) is necessary as the majority of the surgeries cause significant blood loss. Usual monitors like the electrocardiogram, pulse oximetry, end-tidal concentrations of carbon dioxide and the agents that are used should be monitored apart from hourly urine output. If facilities are available parameters that can indicate hypovolemia can be monitored apart from CVP such as delta pulse pressure, systolic pressure variation, etc. If the patient has cardiac abnormalities pulmonary artery catheter can be secured, or Transesophageal echocardiogram (TEE) can be monitored.

**Common complications during intraoperative period**

Commonly complications occur during induction, intubation and tumor manipulation as these procedures stimulate the release of substances. Common cardiovascular complications that happen in these patients are changes in blood pressure and heart rate rather than abnormalities in the rhythm of the heart.

**Hypertension:** It should be treated first with increasing the depth of anesthesia [2]. If it still doesn’t respond then use short acting β – blockers or 5 – HT 2 receptor blockade with ketanserin [25] or octreotide or lanreotide.

**Hypotension:** It can occur in this surgery because of sudden loss of blood or release of substances. So first the monitors should be checked for any hypovolemia had occurred, and it should be corrected. If still it is not resolving then decrease the depth of anesthesia. If still, it is not responding then boluses of octreotide (10 µg/ml) or lanreotide should be given. Administration of octreotide stabilizes the blood pressure within ten minutes if it is due to the release of physiologically active substances. When there is hemodynamic instability, it is always better to halt the surgery temporarily and stabilize the patient and then restart the operation. The other drugs that can be used with variable results are vasopressin and angiotensin. sympathomimetics should be avoided as they can stimulate the release of substances from the tumor. Some authors also used aprotinin with success, but the literature reviews it with varied opinion [2,8].

**Flushing:** It commonly occurs in the upper part of the body such as upper chest and neck spreading to face, upper arms. Flushing should be considered as a warning sign of a potential cardiovascular instability [10,26]. It responds to a bolus of octreotide.

**Bronchospasm:** β-agonists should be avoided as these can stimulate the release of substances from the tumor. A bolus or infusion of octreotide can correct bronchospasm. The other drugs that can be tried are antihistaminics and ipratropium bromide.

**Hyperglycemia:** This can occur due to the high levels of serotonin in the blood. So blood sugar should regularly be monitored intraoperatively and should be treated with insulin infusion if necessary.

**Postoperative management**

Increased levels of serotonin causes delayed awakening of patients from anesthesia. So these patients should be monitored extensively in the post-operative period like that of the intraoperative period. So
these patients should be observed in a high dependency unit. Preoperative octreotide should be tapered over a period of a week. The patient should be brought to the euvoletic state. All electrolyte abnormalities should be corrected. Proper analgesia should be given either in the form of patient controlled intravenous analgesia (commonly with fentanyl) or regional technique such as an epidural.

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