

## RESEARCH ARTICLE

# Somatostatin Analogues Do Not Prevent Carcinoid Crisis

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### Abstract

**Background:** Carcinoid crisis is a life-threatening syndrome of neuroendocrine tumors (NETs) characterized by dramatic blood pressure fluctuation, arrhythmias, and bronchospasm. In the era of booming anti-tumor therapeutics, this has become more important since associated stresses can trigger carcinoid crisis. Somatostatin analogues (SSTA) have been recommended for prophylactic administration before intervention procedures for functioning NETs. However, the efficacy is still controversial. The aim of this article is to review efficacy of SSTA for preventing carcinoid crisis. **Materials and Methods:** PubMed, Cochrane Controlled trials Register, and EMBASE were searched using 'carcinoid crisis' as a search term combining terms with 'somatostatin'; 'octreotide'; 'lanreotide' and 'pasireotide' until December 2013. **Results:** Twenty-eight articles were retrieved with a total of fifty-three unique patients identified for carcinoid crisis. The most common primary sites of NETs were the small intestine and respiratory tract. The triggering factors for carcinoid crisis included anesthesia/surgery (63.5%), interventional therapy (11.5%), radionuclide therapy (9.6%), examination (7.7%), medication (3.8%), biopsy (2%) and spontaneous (2%). No randomized controlled trials (RCTs) were identified and two case-control studies were included to assess the efficacy of SSTA for preventing carcinoid crisis by meta-analysis. The overall pooled risk of perioperative carcinoid crisis was similar despite the prophylactic administration of SSTA (OR 0.44, 95% CI: 0.14 to 1.35,  $p=0.15$ ). **Conclusions:** SSTA was not helpful for preventing carcinoid crisis based on a meta-analysis of retrospective studies. Attentive monitoring and careful intervention are essential. Future studies with better quality are needed to clarify any effect of SSTA for preventing carcinoid crisis.

**Keywords:** Carcinoid crisis - neuroendocrine tumors - SSTA - prophylaxis

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### Introduction

Neuroendocrine tumors (NETs) are a group of heterogeneous tumors that originate from neuroendocrine cells throughout the body (Zeng et al., 2013). Recently, NETs have drawn much attention due to the rapidly rising incidence and relatively benign prognosis (Yao et al., 2008).

Carcinoid crisis is a possible fatality syndrome and mostly occurred in foregut (including respiratory tract, thymus, stomach, duodenum, and pancreas) and midgut (including small intestine, appendix, and right colon) NETs (Tomassetti et al., 2001). The mechanism is associated with the overwhelming release of serotonin and other vasoactive substances such as histamine, prostaglandins, kallikrein, bradykinin (de Vries et al., 2002). Carcinoid crisis is thought as an exacerbation of carcinoid syndrome and the main symptoms include profound flushing, diarrhea, hemodynamic instability (hypotension and rarely hypertension), bronchospasm, tachycardia, and mental abnormalities from light-headedness to coma lasting hours or even days. (Modlin et al., 2010) Rarely, acute renal failure, acute severe pulmonary oedema and coronary artery spasm have also reported to be associated

with carcinoid crisis. (Parry et al., 1996; Erdem et al., 2010; Shah et al., 2012) The incidence of carcinoid crisis varies between different settings of outbreak. During abdominal operations, the incidence of carcinoid crisis was as high as 24% according to a recent study. (Massimino et al., 2013) The occurrence of crisis varied between 1.1% and 36% during the hepatic artery embolization (HAE) treatment for liver metastasis of NETs (Lewis et al., 2012; Lipshutz et al., 2012). The frequency was about 0.5% in radiofrequency ablation (Gillams et al., 2005). Kweekeboom reported the occurrence of carcinoid crisis was about 1% after peptide receptor radionuclide therapy in 510 patients. (Auernhammer and Goke, 2011) Carcinoid crisis can be engendered by anesthesia, medication (chemotherapy, or radiopharmaceuticals) and various invasive procedures. (Tomassetti et al., 2001) It is worth noting that the event can even occur in apparently symptomatic-stable patients and be provoked by a simple biopsy from the tumor body. (Bissonnette et al., 1990; Karmy-Jones and Vallieres, 1993; Turaga and Kvols, 2011) With the wider use of medication and invasive procedures for the diagnosis and treatment of NETs, carcinoid crisis has become of greater importance.

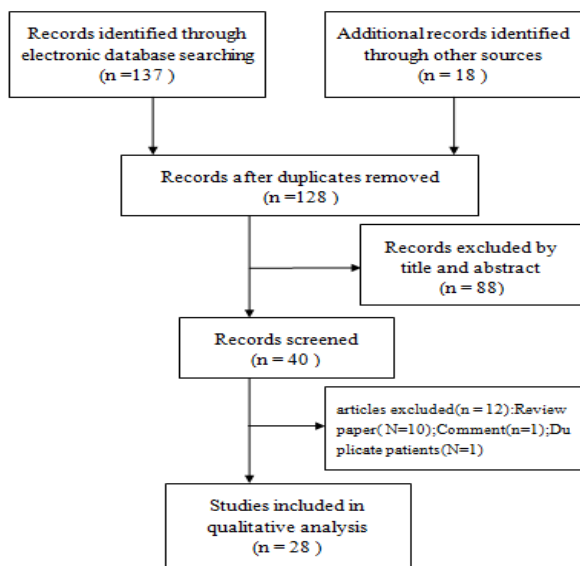
Complicated preparatory regimens were used to

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prevent the onset of carcinoid crisis such as somatostatin analogues, corticosteroids and anti-histaminic drugs. (Holdcroft, 2000) Somatostatin analogues can inhibit hormone secretion and lower the level of peripheral serotonin. (Kvols et al., 1986) Theoretically, Somatostatin analogue should be helpful in preventing carcinoid crisis. (Kvols et al., 1985) Different methods for prophylactic administration of somatostatin analogues are proposed. K. Oberg and colleagues recommend a bolus dose of 250-1000µg octreotide before invasive procedures depending on the stability of NETs symptoms and previous treatments. (Oberg et al., 2004) Ramage and colleagues advocate a constant intravenous infusion of octreotide at a dose of 50mg/h for 12h prior to and at least 48h after surgery for symptomatic patients in 2005. (Ramage et al., 2005) Furthermore, the authors raise cautions for carcinoid crisis in asymptomatic patients and suggest constant preparation of somatostatin analogues before interventional procedures in 2012. (Ramage et al., 2012) Nevertheless, the efficacy regarding the prophylactic usage of SSTA has not been fully assessed and the schemes are generally based on the authors' personal experience. So we intended to perform a systemic analysis to clarify issues about this topic.

**Materials and Methods**

We searched PubMed, Cochrane Controlled trials Register and EMBASE until December 2013 by adopting the following strategy “ (carcinoid crisis) AND (somatostatin or octreotide or lanreotide or pasireotide)”. Two authors independently searched the relevant publications and reviewed the identified studies by the literature search. References from reviews were manually searched to identify additional studies which were missing from the computer-assisted strategy. All carcinoid crisis cases were included. Repetitive cases were excluded. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. (Moher et al., 2009).



**Figure 1. Flow Diagram-selection of Studies**

**Statistical Analysis**

Software Revman 5.1 (provided by the Cochrane Collaboration, Oxford, UK) was used for meta-analysis. Fixed effects model was performed. Statistical significance between trials was evaluated by the Cochran Chi-square test and defined at a P value less than 0.05.

**Description of studies**

We identified 155 references from electronic searches of Pubmed (n=50), The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (n=0), EMBASE (n=87) and other sources (hand-search of the reference list of reviews) (n=18). We excluded 27 duplicate references (Figure 1). We were unable to identify any randomized or quasi-randomised clinical trial suitable from the retrieved references. Twenty-eight articles were retrieved and two retrospective case-control studies were included for meta-analysis.

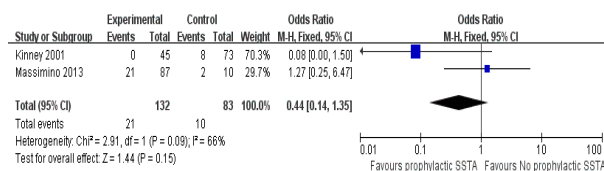
**Results**

Fifty-three carcinoid crisis cases from twenty-eight articles were reported in the literature from 1987 to November 2013. (Ahlman et al., 1987; Marsh et al., 1987; Roy et al., 1987; Ahlman et al., 1988a; Ockert and White, 1988; Darby et al., 1990; Debas and Mulvihill, 1994; Deguchi et al., 1994; Parry et al., 1996; Pekarek et al., 1997; Balestrero et al., 2000; Janssen et al., 2000; Kharrat and Taubin, 2003; Zimmer et al., 2003; Koopmans et al., 2005; Davi et al., 2006; Majeed et al., 2007; Papadogias et al., 2007; De Keizer et al., 2008; McPherson et al., 2009; Sinha et al., 2009; Yazbek-Karam et al., 2009; Fujie et al., 2010; Morrisroe et al., 2012; Raikhelkar et al., 2012; Shah et al., 2012; Massimino et al., 2013; van Diepen et al., 2013) The prophylactic usage of SSTA was diverse between different studies varying from long acting SSTA to continuous somatostatin infusion. Of the 28 patients with known demographic information, 17 cases (60.7%) were men and 11 cases (39.3%) were women. The average age at onset of carcinoid crisis was sixty years. Information about the primary site of NET with carcinoid crisis was available from literature in 22 cases. Most are from forgut and midgut NETs including small intestine 12 cases (54.5%), respiratory tract 7 cases (31.8%) and pancreas 1 cases (4.5%), with the exception of mesenteric NETs 1 cases (4.5%) and pelvic NETs 1 case (4.5%). Various factors had been reported to trigger carcinoid crisis. The distribution of provocative reasons for carcinoid crisis was listed in Table 1. 3.8% cases comprising one bronchus NETs and one pelvis NETs occurred carcinoid crisis without liver metastasis. 11.3% patients outbroke

**Table 1. Triggers for Carcinoid Crisis**

Triggers for carcinoid crisis	Cases (%)
Surgery/anesthesia	33 (63.5%)
Interventional therapy	6 (11.5%)
Radionuclide therapy	5 (9.6%)
Examination*	4 (7.7%)
Medication	2 (3.8%)
Biopsy	1 (2%)
Spontaneous	1 (2%)

\*Examination includes body examination, ultrasound test, colonoscopy



**Figure 2. Effects of Prophylactic SSTA for Carcinoid Crisis**

**Table 2. Perioperative SSTA for Intraoperative Complications**

Study	Intraoperative Complications n/n (%)		p value
	prophylactic SSTA	No prophylactic SSTA	
Massimino (Massimino et al., 2013)	21/87 (24.1)	2/10 (20.0)	0.77
Kinney (Kinney et al., 2001)	0/45 (0)	8/73 (11)	0.023

Carcinoid crisis without previous carcinoid syndrome or with negative 24h urinary 5-hydroxyindoleacetic acid (5-HIAA) test results. Carcinoid heart disease was concurred in 18.9% cases.

#### Meta-analysis for the prophylactic efficacy of SSTA for carcinoid crisis

Two case-control studies were identified comparing prophylactic SSTA for intraoperative complications (including carcinoid crisis) (Table 2). The results however were contradicted. Massimino et al found octreotide LAR and bolus octreotide were insufficient for preventing intraoperative carcinoid crisis in carcinoid patients while Kinney et al reported differently. (Kinney et al., 2001; Massimino et al., 2013) The overall pooled risk showed perioperative carcinoid crisis was similar despite the prophylactic administration of SSTA (OR 0.44, 95% CI: 0.14 to 1.35,  $p=0.15$ ) (Figure 2).

## Discussion

The efficacy of SSTA for preventing carcinoid crisis remains controversial. Evidences are contradicted between different studies. SSTA have been shown to be effective in preventing and reversing carcinoid crisis during clinical experinces. (Parris et al., 1988; Watson et al., 1990). Release of bioactive mediators both under spontaneous and evoked condition such as adrenoceptor agonist and pentagastrin have also been inhibited by SSTA in vitro study. (Ahlman et al., 1988a; 1988b; Lawrence et al., 1990; Westberg et al., 1997). SSTA exert inhibitory role on the secretion of NETs through five subtypes of somatostatin G-protein-coupled receptors (sstr1-5), especially sstr2 and sstr5. (Zimmer et al., 2003; Modlin et al., 2010) The main intercellular mechanisms are mediated by lowering the level of CAMP and calcium concentration. (Modlin et al., 2010) In addition to block the release of mediators, SSTA may also antagonize the peripheral actions of 5-HT and kachykinins on normal cells by inhibit the same intercellular pathway. (Ahlman et al., 1988a; Watson et al., 1990; Wu et al., 2014) The long term inhibitory effect of SSTA has also been studied. (Ahlman et al., 1988a) Chronic usage of SSTA can lower the basal level of 5-HT

which may due to its antiproliferative and anti-angiogenic properties. (Modlin et al., 2010)

On the other hand, both clinical and lab studies have found contrary evidences about the efficacy of SSTA for preventing carcinoid crisis. (Wangberg et al., 1991; Zimmer et al., 2003; Massimino et al., 2013) The possible reasons are investigated. First: the heterogeneity of NETs. The absence of SSTR on NETs cell certainly prevents the effective response to SSTA treatment. Moreover, striking different response between individual NETs cells was observed which indicating different biological features of individual NETs may contribute to the different therapeutic effects of SSTA. (Wangberg et al., 1990; Yucel et al., 2013) Second, SSTA inhibit NETs release in a dose-dependent manner. The protection dosage of SSTA may not be able to outweigh the sudden outbreak of bioactive mediators. (Zimmer et al., 2003) Third, the current form of SSTA such as octreotide and lanreotide mainly act through SSTR2 and SSTR5 which may limit the efficiency of SSTA. The novel developed SSTA (parietotide) which has high affinity to sstr1, sstr2, sstr3 and sstr5, has proved to be more effective than octreotide in treating acromegaly. (Schmid, 2008) Pasireotide may have the potential to be effective in patients unresponsive or refractory to octreotide and lanreotide, as well as in NETs expressing sstr other than SSTR2. (Modlin et al., 2010) Fourth, the release of bioactive mediators of NETs may operate via a different road besides the inhibitory pathways of SSTA. In case of tumor lysis, it is difficult to control the sudden and massive release of mediators with SSTA. (Zimmer et al., 2003).

Although the severity of carcinoid crisis has been noted in the recent guidelines for gastroenteropancreatic neuroendocrine tumors, most studies are about clinical features of NETs. Our study for the first time summarizes the prophylactic efficacy of SSTA for carcinoid crisis. Meta-analysis of the retrospective studies showed prophylactic usage of SSTA was not useful for preventing carcinoid crisis. However the result should be used with discretion. The studies included were both retrospective studies, therefore the quality of evidence were seriously questioned. Also there is lack of a clear definition and a standardized therapeutic regimen for carcinoid crisis. The heterogeneity between different studies may also contribute to the inconsistent results. Further studies are warranted to determine the prophylactic efficacy of SSTA for carcinoid crisis.

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