Octreotide Acetate–Steroid Combination Therapy for Malignant Gastrointestinal Obstruction

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Abstract. *Aim: The Aim of this study was to investigate improvements in symptoms caused by gastrointestinal obstruction following administration of octreotide acetate (Sandostatin®) injection through steroid and opioid administration. Patients and Methods: Patients (n=37) hospitalized with malignant gastrointestinal obstruction were enrolled in the present study. Twenty seven of them were investigated for gastrointestinal symptoms using the Japanese version of the Support Team Assessment Schedule (STAS-J). Results: Octreotide acetate was administered intravenously to all 27 patients. Out of them, 17 showed a marked response, four a good response, and six no response. The overall response rate was 77.8%. Octreotide acetate with a steroid was administered to 19 patients; 13 showed a marked response, four a good response, and two no response at all. Multiple logistic regression analysis showed that that steroid administration improved the efficacy of octreotide acetate after adjusting for infusion dose (p=0.03). Conclusion: Intravenous administration of octreotide acetate with steroid can effectively improve gastrointestinal symptoms due to malignant gastrointestinal obstruction without adverse events.*

Gastrointestinal obstruction in terminally-ill patients with cancer is usually accompanied by gastrointestinal symptoms such as nausea/vomiting and the inability to optimally assimilate nutrients, which significantly reduces patient quality of life. In general, treatment of gastrointestinal obstruction requires for surgical intervention but this is problematic in patients with advanced terminal cancer, due to decreased performance status or cachexia (1, 2). Octreotide acetate (Sandostatin®) is indicated for such cases, and standard administration is performed by continuous subcutaneous injection. However, this method tends to be physically- or mentally-stressfull because each patient already has one infusion route; the addition of a subcutaneous infusion route further constrains patients. It can also become a cause of infection, and further reduce the daily activities of patients. In the present study, we investigated the effect of octreotide acetate administration by intravenous infusion, as well as any additional effect when combined with steroid and opioid administration to improve for gastrointestinal symptoms caused to malignant obstruction.

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Patients and Methods

This retrospective cohort study was conducted at a secondary care facility of the Kawasaki Medical School Hospital. A group of 37 patients hospitalized with malignant gastrointestinal obstruction were enrolled from April 2008 to December 2010 at the Kawasaki Medical School Hospital. All patients had nausea/vomiting and all were administered octreotide acetate intravenously. In this group, 10 were excluded from the study due to disturbance of consciousness, surgery, or a period of administration less than seven days. Five patients underwent surgery according to the surgical indication proposed by Twycross (2).The remaining 27 patients were investigated for the effect of gastrointestinal symptoms. Assessment of symptoms was performed on the first day of administration and one week later using the Japanese version of the Support Team Assessment Schedule (STAS) (3).

The study cohort comprised of 17 men and 10 women (mean age.61.7±13.8 years). Primary cancer foci were gastric cancer in seven, pancreatic cancer in five, uterine cancer in three, colon cancer in three, bile duct cancer in two, ovarian cancer in two, lung cancer in one, rectal cancer in one, unknown primary cancer in one, uterine sarcoma in one, and cancer of the small intestine in one.

Octreotide acetate was administered intravenously for 24 h in all cases. The mean treatment duration was 24.4±26 days (median 15 days). The starting dose of octreotide acetate was 100 μg/day in four patients (two cases had the dosage increased to 300 μg/day), 200 μg/day in seven patients, 300 μg/day in 15 patients (one had the dosage increased to 500 μg/day), and 400 μg/day in one patient. According to the National Council on Compensation Insurance (NCCI) guidelines (4), 300 mg/day as the starting dose are recommended, however, there is no evidence that a 300-mg/day dose is the best starting dose. Hence, we did not start by the starting dose.

Nineteen patients complained of general fatigue. Steroids were concomitantly intravenously administered to these 19 patients (70.4%)

to reduce general fatigue: 10 mg prednisone (n=1), 2 mg dexamethasone (n=5), 4 mg dexamethasone (n=3), 8 mg dexamethasone (n=7), 12 mg dexamethasone (n=1), and 125 mg methylprednisolone (n=2). Table I shows participants' demographics.

Assessment of nausea/ vomiting was performed according to the Japanese version of the Support Team Assessment Schedule (STAS-J) (3). Specifically, the evaluation of nausea/ vomiting was based on the second item of the STAS, which categorizes the effect of symptoms other than pain into five levels, ranging from 0 (none) to 4 (severe and continuous). Assessment of symptoms was performed on the first day of administration and again one week later. A marked response was defined when STAS-J level was 0 (no symptoms) or when patients showed an improvement of two levels or more, a good response was defined as an improvement of a single level and no response was defined as indicating no change in patients' symptoms. The overall effective rate was calculated by summing the number of causes of marked and good response cases divided by the total number of cases. The study was conducted with the approval of the Kawasaki Medical School Ethics Committee (approval number: 332).

Statistical analysis was performed using Fisher's exact probability test, logistic regression as univariate analysis, and multiple logistic regression as multivariate analysis.

A forward logistic regression model was used to determine whether steroid combination therapy, steroid dose, octreotide acetate dose (one week after starting administration), presence or absence of octreotide acetate in the total parenteral nutrition bottle, opioid combination therapy, age, sex, infusion solution dose, use of a nasogastric tube, and ingestion were factors associated with improvement of symptoms following octreotide acetate administration. Titers of dexamethasone and methylprednisolone were converted to titers of prednisone (5).

Variables were tested for collinearity before being entered into the model. A *p*-value of less than 0.2 was chosen in univariate analysis as the criterion for use in the multivariate model. Confidence intervals at the 95% level (95% CI) were reported for the adjusted odds ratios (OR). A *p*-value of less than 0.05 was considered significant.

Table I. *Patients' demographics.*

Characteristic	Patients
All subjects (no.)	27
Gender , no. (%)	
Male	10 (37.0%)
Female	17 (63.0%)
Age, years	61.7±13.8
Steroid combined, no. (%)	
Yes	19 (70.4%)
No	6 (29.6%)
Opioid combined, no. (%)	
Yes	16 (59.3%)
No	11 (40.7%)
Octreotide acetate, μg/day, no. (%)	
500 μg	1 (3.73%)
400 μg	1 (3.73%)
300 μg	15 (55.5%)
200 μg	8 (29.6%)
100 μg	2 (7.40%)
Octreotide acetate , no. (%)	
In TPN bottle	9 (33.3%)
Not in TPN bottle	18 (66.7%)
Dose of steroid, mg/day , no. (%)	
Prednisone 10 mg	1 (5.26%)
Dexamethasone 2 mg	5 (26.3%)
Dexamethasone 4 mg	3 (15.8%)
Dexamethasone 8 mg	7 (36.8%)
Dexamethasone 12 mg	1 (5.26%)
Methylprednisolone 125 mg	2 (10.5%)
Use of nasogastric tube, no. (%)	
Yes	8 (29.6%)
No	19 (70.4%)
Ingestion, no. (%)	
Yes	12 (44.4%)
No	15 (55.6%)
Dose of infusion solution, ml/day, no. (%)	
500 ml	4 (14.8%)
1,000 ml	12 (44.4%)
1,500 ml	7 (25.9%)
2,000 ml	3 (11.1%)
2,500 ml	1 (3.70%)

TPN: Total parenteral nutrition; data are mean±SD.

Results

Table II shows the efficacy of octreotide acetate therapy. In the 27-patient cohort, a marked response was observed in 17 patients, a good response in four, and no response in six, for an overall response rate of 77.8%. Out of the 19 patients concomitantly administered steroids, 13 showed a marked response, four showed a good response, and two had no response. On the other hand, out of the eight patients not administered steroids, four showed a marked response and four showed no response. The overall response rate for the non-steroid group was 50%, significantly lower than that for the steroid combination group ($p<0.04$)

Opioids were administered to 16 patients (59.3%), and a marked response was observed in nine, a good response in three, and no response in four, for an overall response rate of 75%. On the other hand, out of the 11 patients who did not receive opioids, a marked response was observed in eight, a good response in one, and no response in two, for an overall response rate of 81.8%. There was no significant difference in response observed between the opioid and non-opioid groups ($p=0.53$).

The average infusion volume during administration of octreotide acetate was 1,290±512.1 ml/day (median 1,000 ml/day); 1,230±499 ml in the responding group, and 1,500±547 ml in the non-responding group. Table III shows the results of logistic regression analysis and univariate analysis. Logistic analysis showed that steroid administration significantly increased the efficacy of octreotide acetate (OR 9.81, 95% CI 1.39-69. $p=0.02$). Multiple logistic regression analysis showed that this association remained significant after adjusting for the dose of the infusion solution (OR 9.44, 95%CI 1.25-71.2. $p=0.03$) (Table IV). These results show that steroid administration contributes to symptomatic improvement when combined with octreotide acetate. No adverse events were observed in our study.

Table II. *Efficacy of octreotide acetate therapy for gastrointestinal symptoms.*

Characteristic	A marked or good response	No response
All subjects, no. (%)	21 (77.8%)	6 (22.2%)
Gender [no. (%)]		
Male	7 (25.9%)	3 (11.1%)
Female	14 (51.9%)	3 (11.1%)
Steroid combined, no. (%)		
Yes	17 (63.0%)	2 (7.40%)
No	4 (14.8%)	4 (14.8%)
Opioid combined, no. (%)		
Yes	12 (44.4%)	4 (14.8%)
No	9 (33.3%)	2 (7.40%)
Octreotide acetate, μg/day, no. (%)		
500 μg	1 (3.70%)	0 (0%)
400 μg	1 (3.70%)	0 (0%)
300 μg	12 (44.4%)	3 (11.1%)
200 μg	5 (18.8%)	3 (11.1%)
100 μg	2 (7.40%)	0 (0%)
Octreotide acetate, no. (%)		
In TPN	8 (29.6%)	1 (3.70%)
Not in TPN	13 (48.1%)	5 (18.8%)
Dose of steroid, mg/day, no. (%)		
Prednisone 10 mg	1 (3.70%)	0 (0%)
Dexamethasone 2 mg	5 (18.5%)	0 (0%)
Dexamethasone 4 mg	2 (7.40%)	1 (3.70%)
Dexamethasone 8 mg	6 (22.2%)	1 (3.70%)
Dexamethasone 12 mg	1 (3.70%)	0 (0%)
Methylprednisolone 125 mg	2 (7.40%)	0 (0%)
Use of nasogastric tube , no. (%)		
Yes	6 (22.2%)	2 (7.4%)
No	15 (55.6%)	4 (14.8%)
Ingestion , no. (%)		
Yes	10 (37.0%)	2 (7.4%)
No	11 (40.7%)	4 (14.8%)
Dose of infusion solution, ml/day, no. (%)		
500 ml	4 (14.8%)	0 (0%)
1000 ml	10 (37.0%)	2 (7.40%)
1500 ml	4 (14.8%)	3 (11.1%)
2000 ml	3 (11.1%)	0 (0%)
2500 ml	0 (0%)	1 (3.70%)

TPN: Total parenteral nutrition.

Table III. *Univariate analysis of factors affecting octreotide acetate efficacy.*

	Unadjusted odds ratio	95% CI	*p*-Value
Steroid combined therapy			
No	1 (reference)		
Yes	9.81	1.39-69.0	0.02
Dose of steroid [10 mg (Prednisone conversion) increments]	1.02	0.97-1.56	0.41
Dose of octreotide acetate (100 μg increments)	1.00	0.99-1.01	0.50
Octreotide acetate in the TPN bottle			
No	1 (reference)		
Yes	2.00	0.26-15.2	0.50
Opioid combined therapy			
No	1 (reference)		
Yes	1.64	0.27-10.1	0.60
Age (1-year increments)	0.98	0.91-1.05	0.60
Gender (male or female)			
Female	(reference)		
Male	0.49	0.08-3.03	0.44
Dose of infusion solution (500 ml increments)	1.00	0.99-1.00	0.16
Use of nasogastric tube			
No	1 (reference)		
Yes	0.80	0.11-5.54	0.82
Ingestion			
No	1 (reference)		
Yes	1.74	0.27-11.3	0.56

TPN: Total parental nutrition.

Table IV. *Multivariate analysis of factors affecting octreotide acetate efficacy.*

	Adjusted OR	95% CI	*p*-Value
Steroid combined therapy			
No	1 (reference)		
Yes	9.44	1.25-71.2	0.03
Dose of infusion solution (500 ml increments)	1.00	0.99-1.00	0.22

Discussion

Octreotide acetate (6) is an analogue of somatostatin and is indicated for pituitary gigantism. In October 2004, it was approved for patients with malignant bowel obstruction in advanced and recurrent cancer in Japan. Currently, the use of octreotide acetate for such patients is very popular.

Maeno *et al*. (7) reported that out of 130 patients with advanced terminal cancer, bowel obstruction was observed in 13 cases (10%), and 12 of these were complicated by peritoneal carcinomatosis. The average survival from the time of diagnosis of malignant bowel obstruction was 45.5 days, indicating a very poor prognosis. Subjective assessment of palliative care patients is often difficult. The STAS scale is a surrogate measurement scale developed in England by Higginson and is often used in hospice and palliative care scenarios (8). This scale is advantageous because it does not burden patients unduly. The Japanese version, STAS-J, was published in 2004 (3) and is considered reliable and useful.

Bowel expansion as a consequence of obstruction increases gut lumen volume and secretion of intestinal fluid. As a result, the intestinal tract becomes further extended and abdominal pain and other symptoms emerge. Octreotide acetate has been reported to reduce the secretion of digestive juices, reduce peristalsis, and affect water and electrolyte absorption (9). Khoo *et al*. reported that continuous subcutaneous injection of octreotide acetate (dosage: 0.1-0.6 mg/day) in patients refractory to conventional therapies remedied symptoms of nausea/ vomiting in 58.3% of patients (14/24), while reducing them in 16.7% of patients (4/24) (10). Since no adverse events were observed, octreotide acetate was thought to be beneficial for patients with malignant obstruction. In the present study, octreotide acetate–steroid combination therapy had a response rate of 89.4%, whereas octreotide monotherapy had a significantly lower response rate of 50%. Laval *et al*. reported that in a randomized controlled study, symptoms were relieved in 68% of otreotide-treated cases *versus* 33% among placebo-treated (methylprednisolone) patients (11). These data support our assessment that octreotide acetate–steroid combination therapy is useful for malignant gastrointestinal obstruction.

The mean duration of octreotide acetate administration in this study was 24.4±26 days (median 15 days). Octreotide acetate administration is not too expensive because of the limited administration period.

Indication of octreotide acetate in the U.S. is limited to acromegaly, carcinoid tumor, and vasoactive intestinal peptide (VIP) producing tumor, with the drug administered intravenously or by subcutaneous injection (12). In the present study, all patients were administered octreotide acetate intravenously because subcutaneous administration for patients with gastrointestinal obstruction was considered to be too stressful and every patient already had an infusion route, an additional subcutaneous infusion route would further constrain patients. In our study, no adverse events were observed, and the effective rate was considered satisfactory at 77.8%.

The use of the octreotide acetate for reduction of the symptoms of malignant bowel obstruction is the standard therapy according to NCCI, European Association for Palliative Care (EPAC) and Journal of Clinical Oncology (JCO) guide lines (4, 13, 14). According to JCO guide lines, steroid is not recommended in the therapy of malignant bowel obstruction (14). Study of the combination therapy of octreotide acetate and steroid in a randomized controlled trial is needed for a high level evidence. However, this has an ethical problem. We believe that further study is required.

In conclusion, intravenous administration of octreotide acetate improved symptoms of nausea/vomiting in patients with gastrointestinal obstruction. Furthermore, octreotide acetate–steroid combination therapy can effectively improve gastrointestinal symptoms for malignant gastrointestinal obstruction without adverse events.

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Disclosures

None.

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