Efficacy of Octreotide in the Control of Acute Upper Gastrointestinal Bleeding

PINIT KULLAVANIJAYA, M.D.*,
DUANGPORN THONG-NGAM, M.D.**,
NUSONT KLADCHAREON, M.D.*
SURATVADEE MANOTAYA, M.D.*,
VAROCHA MAHACHAI, M.D.*,

Abstract

To evaluate the efficacy and safety of octreotide in the control of acute upper gastrointestinal (GI) bleeding and prevention of rebleeding, the Gastroenterology Unit, Chulalongkorn University Hospital, conducted a prospective open study in patients with acute upper GI bleeding. All patients with acute upper GI bleeding were given octreotide by intravenous infusion. The patients then had endoscopic confirmation within 24 hours, were divided into variceal and non-variceal groups, and then randomly allocated to receive either 48 hours of octreotide infusion or 48 hours of octreotide infusion plus 72 hours subcutaneous injection. Efficacy and safety of octreotide were evaluated during the 5 days observation period.

Forty-three patients with acute upper GI bleeding were treated with octreotide infusion. After endoscopy, 16 patients in the variceal group and 22 patients in the non-variceal group were randomized to receive 48 hours infusion or 48 hours infusion plus 72 hours subcutaneous infusion. Failure to control active bleeding occurred in 11 patients (28.9%) and failure to prevent rebleeding was found in 5 patients (13.2%).

The results showed that the effect of octreotide infusion in controlling acute upper GI bleeding appeared to be not different between the variceal and non-variceal causes. Subcutaneous injection of octreotide for another 72 hours showed no apparent benefit for the prevention of rebleeding.

Key word : Octreotide, Gastrointestinal Bleeding

KULLAVANIJAYA P, MANOTAYA S, THONG-NGAM D, MAHACHAI V, KLADCHAREON N
J Med Assoc Thai 2001; 84: 1714-1720

* Gastroenterology Unit, Department of Medicine,
** Department of Physiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

In the management of acute upper GI bleeding, an effective treatment to control active bleeding and prevent early rebleeding is needed(1, 2). Endoscopic hemostatic therapy is accepted as a definitive and effective therapy for such purposes (3-5). In the situation where an endoscopic facility is not immediately available nor appropriate, effective, safe and simple first line treatment such as drug therapy appears desirable(6).

Vasoactive agents such as vasopressin, somatostatin and octreotide have been used, and both positive and negative results in achieving hemostasis have been reported(7-16).

The objectives of the study were :-

1. To study the efficacy and safety of 48 hours' intravenous infusion of octreotide in the control of acute upper GI bleeding.

2. To evaluate the efficacy and safety of octreotide subcutaneous injection every 8 hours for another 72 hours for the prevention of rebleeding.

MATERIAL AND METHOD

Patients with acute upper gastrointestinal bleeding admitted to the emergency room, Chulalongkorn University Hospital, from Feb 1, 1995 to June 30, 1996 were enrolled in this study.

Inclusion criteria included :

1. Patients with significant upper GI bleeding (as indicated by hematemesis and/ or melena within 48 hours), active significant systemic disturbances (pulse > 100 / min, or systolic blood pressure < 100 mmHg, or hematocrit < 30 per cent or requirement of 2 or more units of blood in the first 24 hours to restore hematocrit).

2. Endoscopic confirmation of the presence of any of the following sources of bleeding : esophagogastric varices, portal hypertensive gastropathy, peptic ulcer, erosive gastritis, or Mallory - Weiss tear within 24 hours of drug infusion.

3. Patient has given verbal or written consent (the patient or his/her legal representative).

Patients were excluded from the study if they were :

1. Patients with acute hemorrhage who had previously received more than 6 units of blood or plasma within 6 hours (failure to control bleeding).

2. Patients who had received injection sclerotherapy within the previous 7 days.

3. Patients who had received other treatment to control the bleeding e.g. balloon temponade or other vasoactive therapy.

4. Patients who had previously entered the study.

Forty-three patients who were recruited into the study received octreotide intravenous infusion at the dose of 50 mcg/hours immediately. The patients were transferred to the Gastroenterology Unit to have endoscopic confirmation 1-23 (average 7.9) hours after octreotide infusion.

When the diagnosis of the cause of acute upper GI hemorrhage was established, the patients were divided into 2 groups; varices (16 patients) and the nonvarices group (27 patients). Then in each group, the patients were randomly allocated to receive either 48 hours of octreotide infusion or 48 hours of octreotide infusion plus 72 hours subcutaneous injection of 100 mcg octreotide every 8 hours. The procedure was randomized by using a sealed envelope technique.

Thus, patients were stratified into 4 main groups :

Group 1. Acute variceal bleeding with 48 hours infusion (9 patients).

Group 2. Acute variceal bleeding with 48 hours infusion plus subcutaneous injection every 8 hours for 3 days (7 patients).

Group 3. Acute non-variceal bleeding with 48 hours infusion (10 patients).

Group 4. Acute non-variceal bleeding with 48 hours infusion plus subcutaneous injection every 8 hours for 3 days (12 patients).

Five patients were excluded from the study after being treated with octreotide for the following reasons : Neoplastic gastric lesion (2 patients), endoscopic therapy given by responsible physician in the presence of inactive bleeding gastric ulcer (2 patients) and Dieulafoy lesion (1 patient).

Blood was sampled for full blood count, clotting screen, biochemistry, ammonia, glucose, as soon as possible, and also on day 1, day 3 and day 5. Blood, plasma, including platelets were transfused according to clinical need to restore vital signs to normal, aiming for hematocrit > 30 per cent. During the 5 day period, the trial was stopped if the criteria of failure was fulfilled. Nonresponders or partial responders to octreotide were treated with other

appropriate treatment as soon as possible. Blood pressure, pulse rate, temperature and respiratory rate were recorded regularly. Any adverse event was observed.

Criteria of failure included :

1. Uncontrollable bleeding at any time during therapy.

2. Require more than 6 units of blood or plasma in any 6 hours during drug therapy.

3. Rebleeding after 48 hours.

The critical end points for determining the efficacy of octreotide in controlling acute upper GI hemorrhage during the 5 day study period were :

1. Incidence and period when active bleeding stopped.

2. Blood transfusion requirement for active bleeding (within 24 hours).

3. Incidence, and time of rebleeding (after 48 hours).

4. Blood transfusion requirement for rebleeding.

5. Need for intervention (i.e. injection sclerotherapy).

All medications, besides the study medication, were recorded in the concomitant medication form. Any coexisting disease or relevant intercurrent medical conditions were also recorded.

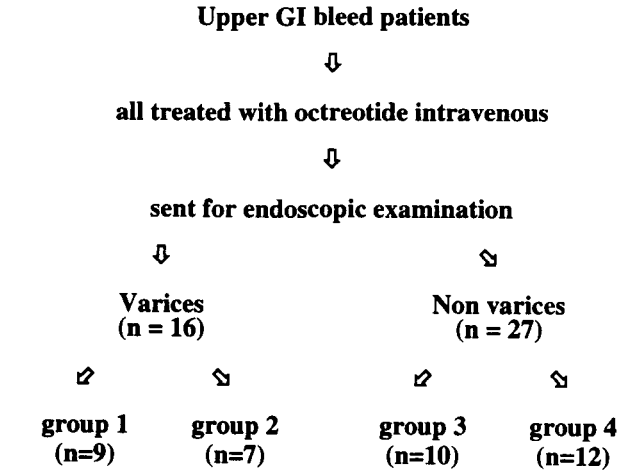
The complete control of bleeding within 48 hours and rebleeding (day 3-5) in both variceal and non-variceal group were described in percentage.

Two groups of patients were analyzed for incidence of uncontrolled bleeding, rebleeding, requirement of blood or plasma transfusion, therapeutic endoscopy, surgery, hospital stay and death by two-way ANOVA.

This project was approved by the Ethical Committee of the Faculty of Medicine, Chulalongkorn University.

RESULTS

The enrolled patients were divided into four groups as presented in the following diagram.



group 1 = 48 hours infusion only.
group 2 = 48 hours infusion plus 72 hours subcutaneous.
group 3 = 48 hours infusion only.
group 4 = 48 hours infusion plus 72 hours subcutaneous.

The age range was from 21-73 years old and there was no statistical difference between each group in these following factors; time from bleeding to admission, time from admission to octreotide use, time from octreotide use to endoscopy, and amount of active bleeding cases at endoscopy. In the variceal bleeding groups (group 1 and 2), 5 of 16 patients (31.2%) failed to achieve hemostas is during the first 48 hours. Of these, 3 patients received endoscopic variceal sclerotherapy (EVS), 1 patient required emergency porto - caval shunt. One patient (group 1) died because of uncontrolled bleeding from gastric varices 27 hours after octreotide infusion. Rebleeding (day 3-5) occurred in 4 patients (25%), 1 patient in the control group (group 1) and 3 patients in the group which received subcutaneous octreotide injection (group 2). These 4 patients also achieved hemostasis by endoscopic variceal ligation (EVL). Units of blood or plasma transfused and days of hospital stay were not statistically different between the two groups.

The non-variceal bleeding group (group 3 and 4) consisted of 10 GU, 3 DU, 4 gastroduodenitis and 5 Mallory-Weiss tear. Six of 22 patients in these 2 groups (17.3%) failed to achieve hemostasis during the first 48 hours. Rebleeding occurred in 1 patient (group 4) while receiving octreotide subcutaneous injection, none in the control group had rebleeding. Hemostasis was achieved in 4 patients after endoscopic injection of epinephrine. The two groups were not different in aspects of blood or plasma transfused and days of hospital stay. One patient (group 3) died of sepsis after a bleeding gastric ulcer was controlled. The clinical outcome of the patients studied is shown in Table 1 and 2.

Octreotide was well tolerated by all the patients studied. No adverse reactions were observed in this trial. Overall success rate is summarized in Table 3.

Hemostasis was achieved by 48 hours intravenous infusion of octreotide in 68.8 per cent of patients with variceal bleeding and 72.7 per cent of patients with non-variceal bleeding. For 5 days treatment, hemostasis was obtained in 43.8 per cent of patients with variceal bleeding and 68.2 per cent of patients with non-variceal bleeding. Subcutaneous injection of octreotide for 72 hours following the initial 48 hours intravenous infusion appeared to be of no apparent benefit, since rebleeding during day 3-5 occurred more in the treatment group than in the control group.

DISCUSSION

Bleeding esophageal varices is one of the main complications of cirrhotic patients with portal hypertension. Even though bleeding may spontaneously stop in about 40-60 per cent of cases, the chance for early rebleeding is about 20-50 per cent with a high mortality rate[2,17].

It is now accepted that therapeutic endoscopy is the procedure of choice for the control of actively bleeding varices[3-5]. Somatostatin and octreotide have been shown to be as effective as vasopressin, terlipressin and therapeutic endoscopy

Table 1. Results of octreotide infusion with and without subcutaneous injection in the variceal bleeding group.

	Group 1* (n=9)	%	Group 2** (n=7)	%	P value
Bleeding					
Bleeding uncontrolled in 48 hours	3	33.3	2	18.6	1.000
Rebleeding (day 3-5)	1	11.1	3	42.8	0.242
Blood or plasma transfusion (unit)					
First 48 hours	1-15	6.7	3-19	7.7	0.734
Day 3-5	0-16	1.88	0-10	4.0	0.461
Therapeutic endoscopy / surgery	3		5		
Hospital stay (days)	5-23	8	5-15	8	1.000
Death	1		0		1.000

* group 1 = 48 hours infusion only

** group 2 = 48 hours infusion plus 72 hours subcutaneous

Table 2. Results of octreotide infusion with and without subcutaneous injection in the non-variceal bleeding group.

	Group 3* (n=10)	%	Group 4** (n=12)	%	P value
Bleeding					
Bleeding uncontrolled in 48 hours	2	20.0	4	33.3	0.646
Rebleeding (day 3-5)	0	0	1	8.33	1.000
Blood or plasma transfusion (unit)					
First 48 hours	0.5-17	4.7	0-11	4.3	0.816
Day 3-5	0.5	0.6	0-5	0.6	0.980
Therapeutic endoscopy / surgery	0		4		
Hospital stay (days)	5-19	6.9	2-10	5.5	0.381
Death	1		0		

* group 3 = 48 hours infusion only
** group 4 = 48 hours infusion plus 72 hours subcutaneous

Table 3. Overall success rate.

	Variceal bleeding (n=16)	%	Non-variceal bleeding (n=22)	%
Day 1-2	11/16	68.8	16/22	72.7
Day 3-5	7/11	63.6	15/16	93.8
Total (5 days)	7/16	43.8	15/22	68.2

in the control of acute variceal bleeding with minimal side effects[8-15]. In this study, the success rate of 68.8 per cent in the complete control of variceal bleeding during the first 48 hours using intravenous infusion of octreotide, was comparable to other studies which reported hemostatic rates of 50 to 85 per cent.

In the management of upper gastrointestinal bleeding from non-variceal causes, endoscopic hemostatic therapy is also accepted as the most effective method to control active bleeding[1,7].

Somatostatin and octreotide have been tried in several studies, both have been found to be effective in arresting bleeding in 80-100 per cent of patients with bleeding peptic ulcers, and in about 80 per cent of patients with superficial lesions. The hemostatic rate of our non-variceal bleeding cases of 72.7 per cent during the first 48 hours is considered satisfactory since we enrolled only patients with active and severe bleeding[7]. Somatostatin was efficacious for peptic ulcer bleeding and showed a trend toward efficacy for non-peptic ulcer bleeding[17].

The duration of octreotide usage was usually 1-2 days in most of the series[7-15]. In this study, in order to evaluate the effect of the drug on the prevention of rebleeding, octreotide was given for another 72 hours in two groups of patients while the other two groups served as control. This regimen was probably not effective as rebleeding occurred more in the treatment group than in the control group.

A possible explanation for the inefficacy of octreotide to prevent rebleeding is that subcutaneous injection may not be as effective as intravenous injection, eventhough efficacy of subcutaneous injection of octreotide has been reported[11]. With the increasing use of endoscopic hemostasis, drug therapy alone for prevention of rebleeding is probably not recommended except in combination with endoscopic hemostasis[12].

Octreotide is a safe and effective drug in controlling acute upper GI bleeding and there appears to be no difference between the variceal and non-variceal causes. Octreotide may be useful either as an adjunct treatment before endoscopy or when

endoscopy is unsuccessful, contraindicated, or unavailable. For prevention of rebleeding, a possible role for octreotide appears to be as an adjunct to endoscopic hemostasis. But the benefit in this aspect needs further investigation.

ACKNOWLEDGMENT

The authors wish to thank their colleagues, the nursing staff of their departments for their collaboration and Sandoz Ltd. for providing Sandostatin (Octreotide®).

(Received for publication on August 21, 2000)

REFERENCES

1. NIH consensus conference on therapeutic endoscopy and bleeding ulcers. JAMA 1989; 262: 1369-72.
2. Silverstein FE, Feld AD, Gilbert DA. Upper gastrointestinal tract bleeding. Arch Intern Med 1981; 41: 322-7.
3. Hassan F, Levine BA. The role of endoscopic sclerotherapy in the management of esophageal varices. Dig Dis 1992; 10 (Suppl 1): 38-45.
4. Williams SGJ, Westaby E. Management of variceal hemorrhage. BMJ 1994; 308: 1213-7.
5. Williams SGJ, Westaby D. Recent advances in the endoscopic management of variceal bleeding. Gut 1995; 36: 647-8.
6. Burroughs AK, Mezzanotte G, Phillips A, Mc Cormick A, Mc Intyre N. Cirrhotics with variceal hemorrhage : The importance of the time interval between admission and the start of analysis for survival and rebleeding rates. Hepatology 1989; 9: 801-7.
7. Lin HJ, Perng CL, Wang K, Lee CH, Lee SD. Octreotide for arrest of peptic ulcer hemorrhage : A prospective, randomized controlled trial. Hepato-Gastroenterology 1995; 42: 856-60.
8. Silvain C, Carpatier S, Santerean D, et al. Terlipressin plus transdermal nitroglycerin *vs* octreotide in the control of acute bleeding from esophageal varices : A multicenter randomized trial. Hepatology 1993; 18: 61-5.
9. Planus R, Quer JC, Boix J, et al. A prospective randomized trial comparing somatostatin and sclerotherapy in the treatment of acute variceal bleeding. Hepatology 1994; 20: 370-5.
10. Burroughs AK. Somatostatin and octreotide for variceal bleeding. J Hepatology 1991; 13: 1-4.
11. Besson I, Ingrand P, Person B, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. N Engl J med 1995; 333: 556-60.
12. Sung JJY, Chung SCS, Lai CW, et al. Octreotide infusion or emergency sclerotherapy for variceal haemorrhage. Lancet 1993; 342: 637-41.
13. Imperiale TF, Teran JC, Mc Cullough AJ. A meta-analysis of somatostatin *versus* vasopressin in the management of acute esophageal variceal hemorrhage. Gastroenterology 1995; 109: 1289-94.
14. Burroughs AK, Mc Cormick PA, Hughes MD, Sprengers D, D'Heygere F, Mc Intyre N. Randomized, double-blind, placebo-controlled trial of somatostatin for variceal bleeding. Gastroenterology 1990; 99: 1388-95.
15. Walker S, Kreichganer HP, Bode JC. Terlipressin *vs* Somatostatin in bleeding esophageal varices : A controlled, double-blind study. Hepatology 1992; 15: 1023-30.
16. Imperiale TF, Birgisson S. Somatostatin or octreotide compared with H2 antagonists and placebo in the management of acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. Ann Intern Med 1997; 15; 127: 1062-71.
17. Dombal FT Clarke JR, Clamp SE, Malizia G, Kotwal MR, Morgan AG. Prognostic factors in upper GI bleeding. Endoscopy 1989; 18 (Suppl 2): 6-10.

ประสิทธิภาพของยาออคทรีโอไทด์ ในการรักษาภาวะเลือดออกจากทางเดินอาหารส่วนต้น

พินิจ กุลละวณิชย์, พ.บ., สุรัสวดี มโนทัย, พ.บ.*,*
*ดวงพร ทองงาม, พ.บ.**, วโรชา มหาชัย, พ.บ.*, นุสนธิ์ กลัดเจริญ, พ.บ.**

เพื่อต้องการประเมินถึงประสิทธิภาพและความปลอดภัยของยาออคทรีโอไทด์ ในการรักษาผู้ป่วยที่มาด้วยเรื่องเลือดออกจากทางเดินอาหารส่วนต้นเฉียบพลัน รวมทั้งผลของยาที่มีต่อการป้องกันการเกิดเลือดออกซ้ำ ในผู้ป่วยที่มารับการรักษาที่หน่วยโรคระบบทางเดินอาหาร โรงพยาบาลจุฬาลงกรณ์ โดยผู้ป่วยทุกรายที่เข้าร่วมโครงการศึกษานี้จะได้รับการตรวจส่องกล้องทางเดินอาหารส่วนต้นภายใน 24 ชั่วโมง เพื่อวินิจฉัยแบ่งกลุ่ม เป็น 2 กลุ่มคือ กลุ่มแรกมีสาเหตุจากเส้นเลือดขอด และกลุ่มที่สองมีสาเหตุอื่นที่ไม่ใช่จากเส้นเลือดขอด ทั้งสองกลุ่มนี้จะได้รับการสุ่มโดยวิธีเปิดซอง ให้การรักษาโดยใช้ยาออคทรีโอไทด์หยดทางหลอดเลือดดำเป็นเวลา 48 ชั่วโมง หรือได้ยาออคทรีโอไทด์หยดทางหลอดเลือดดำ 48 ชั่วโมงร่วมกับฉีดเข้าชั้นใต้ผิวหนังอีก 72 ชั่วโมงต่อมา ดูประสิทธิภาพของยาในการทำให้เลือดหยุดออกที่ 48 ชั่วโมง และผลของการป้องกันเลือดออกซ้ำในวันที่ 5

ผลการศึกษามีผู้ป่วยเข้าร่วมโครงการทั้งสิ้น 43 ราย แบ่งเป็นกลุ่มมีสาเหตุจากเส้นเลือดขอด 16 รายและกลุ่มที่มีสาเหตุอื่นไม่ใช่จากเส้นเลือดขอด 22 ราย พบว่ายาออคทรีโอไทด์สามารถหยุดเลือดที่ออกได้ดีในทั้งสองสาเหตุ โดยมีผู้ป่วยที่ไม่สามารถหยุดเลือดออกได้ (failure) ทั้งสิ้น 11 ราย คิดเป็น 28.9% และไม่สามารถป้องกันการเกิดเลือดออกซ้ำในผู้ป่วย 5 ราย คิดเป็น 13.2% ไม่มีผู้ป่วยรายใดเกิดผลข้างเคียงจากยา ผลของการรักษาในกลุ่มที่ได้ยาหยดทางหลอดเลือดดำอย่างเดียวหรือกลุ่มที่ใช้ร่วมกับการฉีดเข้าชั้นใต้ผิวหนังไม่มีความแตกต่างกัน

สรุปการศึกษา ประสิทธิภาพของยาออคทรีโอไทด์ ในการรักษาภาวะเลือดออกจากทางเดินอาหารส่วนต้นได้ผลดีไม่ต่างกันทั้งจากสาเหตุเส้นเลือดขอด หรือไม่ใช่เส้นเลือดขอด โดยมีความปลอดภัยในการใช้ยานี้

คำสำคัญ : ออคทรีโอไทด์, เลือดออกจากทางเดินอาหารส่วนต้น

พินิจ กุลละวณิชย์, สุรัสวดี มโนทัย,
ดวงพร ทองงาม, วโรชา มหาชัย, นุสนธิ์ กลัดเจริญ
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 1714–1720

* หน่วยโรคระบบทางเดินอาหาร, ภาควิชาอายุรศาสตร์,
** ภาควิชาสรีรวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330