# Comparison of Long-Acting Somatostatin Analogue (SMS 201-995) and Balloon Tamponade in Treatment of Acute Variceal Hemorrhage

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***Özet:*** *Bu çalışmada kanayan özefagus varislerinin kontrolunda Sengstaken-Blakemore balon tamponadı ile somatostatin analoğu olan SMS 201-995'in etkisini karşılaştırdık. 19 özefagus varis kanamalı hasta randomize olarak iki gruba ayrıldı. Grup A'daki hastalara 50 mg, SMS 201-995 başlangıç bolusunu takiben 50 mg/saat infüzyona geçildi. Grup B'deki hastalar Sengstaken-Blakemore tüpü ile tedavi edildi. Grup A'da 12, Grup B'de 7 hasta vardı. İki grup arasında sarılık ve alkol öyküsü, protrombin zamanı açısından fark yoktu. SMS 202-995 verilen hastaların 9'unda (%75), Sengstaken balon tamponad uygulanan hastaların 5'inde (%71,42), tedavinin ilk 4 saatinde primer hemostaz sağlandı. Grup A'da 7 hastada (%58,33), Grup B'de 5 hastada (%57,14), 48. saat sonu kalıcı hemostaz sağlandı. Sengtaken balon tamponadı ile tedavi edilen hastaların 5'inde göğüste dolgunluk hissi görülürken SMS 201-995 verilen hastalarda komplikasyon görülmedi. İki grup arasında transfüzyon sayısı, primer hemostaz ve kanamanın kesin kontrolu bakımından anlamlı fark bulunmadı.*

*Sonuçta, bu çalışmada SMS 201-995 infüzyonu Sengstaken balon tamponad kadar etkili bulundu. SMS 201-995 ile tedavi edilen hastalarda komplikasyon görülmedi.*

**Anahtar kelimeler:** Özefagus varis kanaması, somatostatin, balon tamponadı.

***Summary:*** *The present trial compared the effectiveness and complications of intravenous long-acting somatostatin analogue (SMS 201-995) and Sengstaken-Blakemore balloon tamponade in treatment of variceal bleeding. Ninteen consecutive patient with esophageal variceal bleeding were randomly assigned to treatment with a 50 g SMS 201-995 invtarvenous (i. v.) bolus and than continuous infusion of at 50 g/h (group A) or to treatment with Sengstaken-Blakemore tube (group B). 12 patients were assigned to group A, and 7 to group B. No difference in prothrombin time, alcohol intake, joundice were found between the groups, primary haemostasia within the first 4 h of treatment was obtained in 9 (75%) of the patients receiving SMS 201-995 and in 5 (71.42%) of those receiving Sengstaken balloon tamponade. Bleeding was controlled over a 48 h period 7 patients (58.33%) in group A and 5 patients (57.14%) in group B. 5 of Sengstaken balloon tamponade-treated patients developed discomfort. Two of the 7 patients treated with balloon tamponade died due to hepatic encephalopathy.*

*No significant differences in primary haemostasia, definitive controlling of bleeding, number of transfusions were found between the two groups. In can be concluded that SMS 201-995 is an effective drug for the management of variceal bleeding. Its efficiacy is comparable to balloon tamponade appear to be similar. In addition it is safer and entails a lower risk of side effects and complication than balloon tamponade.*

**Key words:** Long-acting, somatostatin analogue (SMS 201-995), balloon tamponade, senstaken blackemore, variceal bleeding.

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Vasopressin administration is an established form of medical treatment in patients with portal hypertension and bleeding oesophageal varices; it effectively reduces the splanchnic blood flow and lowers the portal venous pressure (1,2). However, it is also known to elicit peripheral vasoconstriction, a rise in systemic arterial pressure, and a decrease in cardiac output (1,2). In view of these adverse haemodynamic effects induced by vasopressin together with other side effects such as diarrhoea and angina, alternative pharmacological agents need to be considered in the treatment of patients with bleeding oesophageal varices. In this respect, somatostatin may be of interest, since it is known to reduce hepatic blood flow both in healthy subjects (3,4) and in patients with liver cirrhosis (2,5). In addition, several reports indicate that somatostatin may lower portal venous pressure in patients with cirrhosis (2,5,6), whereas other studies have been unable to confirm this finding (4). However, the short biological half-life (2-3 min) of somatostatin limits its possible usefulness as a therapeutic agent in patients with oesophageal varices. Recently, an octapeptide somatostatin analogue (SMS 201-995) with physiological effects similar to that of regular somatostatin but with a biological halflife of 1-2 h has been synthesized (7,8). In our clinic, we were demonstrated that administration of SMS 201-995 reduced the portal vein blood flow by doppler-sonography9.

The aim of treatment of esophageal variceal bleeding is rapid haemostasia and the prevention of haemorrhage recurrence. Both surgery and endoscopic sclerotherapy have proved effective. Ballon tamponade and vasoactive drugs have also proved effective as temporary methods since the incidence of recurrence is high after treatment is discontinued (10-15). Esophageal balloon tamponade is uncomfortable for the patient and is sometimes responsible for a number of severe complications (10-13). Somatostatin has been shown to be similar to vasopressin and injection sclerotherapy for controlling acute variceal bleeding (16-19). Although some data from the literature suggest that balloon tamponade could be more effective than somatostatin, no controlled studies comparing these two treatments hav ebeen carried out. The aim of this randomized study was to compare the efficacy between SMS 201-995 and balloon tamponade in the treatment of acute variceal bleeding.

## MATERIAL and METHODS

Patients admitted consecutively to the hospital with diagnosis of variceal bleeding, were included in this study. They were frequired to fulfil one of the following criteria: a) Active bleeding from varices seen during endoscopy, early after admission. b) Rebleeding from varices while in the hospital (red haematemesis or frequent melaenas with haemodynamic changes and decrease of haematocrit), in patients without actively bleeding varices on admission. c) Patients with suspected esophageal varices (past history and physical signs) and in need of urgent treatment for massive bleeding were initially included until confirmed on endoscopy.

The following criteria for exclusion were established: a) Anatomical defects preventing easy insertion of the Sengstaken tube. b) Patient refusal to be treated with balloon tamponade. c) Methodological errors after treatment had been started. d) Patients with gastric varices. e) Delayed discovery of another bleeding lesion in patients included without early endoscopy because of massive bleeding.

Patients were divided with a table of random numbers into two groups to be treated with somatostatin or balloon tamponade with Sengstaken tube.

Upper gastrointestinal bleeding was diagnosed only if haematemesis and/or melaenas were confirmed by the hospital staff. Etiology of bleeding was established by endoscopy, performed within 12 h after admission. Esophageal varices were considered the source of bleeding if a jet or oozing haemorrhage was observed, if the varices showed recent bleeding stigmata (erosions or clots), of if they were the only potential cause of bleeding found on endoscopy.

The following and points were established:

1) Death before any of the following and points

were achieved.

2) Continued bleeding after 4 h treatment.

3) Massive bleeding within the first 4 h of treatment.

4) Rebleeding after initial haemostasia and more than 4 h of treatment, but before sclerotherapy was performed.

5) Complications of either somatostatin or balloon tamponade requiring the discontinuation of treatment.

6) Elective sclerotherapy session the morning after admission, provided haemostasia was achieved within 4 h of treatment.

7) After 24 h of haemostasia, if for any reason, sclerotherapy was not performed.

End points 6 and 7 were required before considering the treatment a success. Treatment failure and alternative therapy was considered if any or the and points 1 to 5 were reached.

All patients were admitted to the hospital for gastrointestinal bleeding. The patients received the following standard treatment: Volume replacement with intravenous fluids and blood to maintain haematocrit above 30%. Ranitidine 50 mg i. v. three times a day. Oral lactulose 30 ml three times a day. Each patient received a non-inflated Sengstaken-Blakemore tube to be used as a nasogastric tube, and for balloon tamponade in group B patients.

Group A: SMS 201-995 was administered continuously i. v. at 250 μg/h after an initial bolus of 50 mg. If haemostasia was not achieved after 3.5 h on somatostatin, a second bolus of 50 μg was given. Thirty min later, in case of failure, the Sengstaken tube was inflated, and the SMS 201-995 infusion with drawn.

Group B: Three lumen Sengstaken-Blakemore tubes were used. After the balloons were checked for leaks they were inserted into the stomach through a nasal orifice. The gastric balloon was inflated with 240-300 ml of air and pulled up to the cardias. The tube was fixed to the nose. The esophageal balloon was inflated with 80-120 ml of air according to the patient's tolerance.

Patients were randomized and treated immediately following fulfillment of the inclusion criteria.

Patients were monitored for vital signs. The ECG was also occasionally monitored. The patients received gastric washings with saline every 30 min. Haematocrit, haemoglobin, urea, glocuse creatinine and electrolytes in serum and urine were determined every 12 h, and following any seruous bleeding episode. A chest X-ray was performed on admission and at the and of treatment.

Initial haemostasia. When a clear or ground-coffee gastric aspirate was obtained, and the patient was haemodynamically stable.

Rebleeding: Bloody gastric aspirate or frequent melaenas with haemodynamic changes and decreases of haematocrit, after initial haemostasia.

Primary haemostasia: Initial haemostasia achieved and lack of relapses.

Massive bleeding: Haemodynamic stability was not achieved at admission or more than 1000 ml/h of i. v. fluids was needed for it to be maintained.

Haemodynamic stability: The presence of all of the following: a) systolic blood pressure over 100 mmHg; b) heart rate less than 100 beats per min; c) urine output over 35 ml/h; and d) no peripheral signs of low perfusion.

A protocol regarding past history and physical examination, endoscopy, blood tests, ultrasound, treatment and follow up allowed us to compare the two groups and the results of treatment.

The efficacy of the two treatments was assessed by comparing the proportion of initial hameostasia achieved, number of patients with successful treatment and complications.

**RESULTS**

No statistically significant difference between

**Table I:** Clinical data of the patients.

| | SMS 201-995 | Balloon Tamponade |
|---|---|---|
| No | 12 | 7 |
| Age | 51.5 ± 3.2 | 57 ± 3.1 |
| Sex (F/M) | 7/5 | 5/2 |
| Jaundice | 8 | 5 |
| Child's classification | | |
| A | 2 | 1 |
| B | 8 | 4 |
| C | 2 | 2 |

the two groups in relation to age, sex or etiology of cirrhosis (Table 1). In addition, there were no significant differences between the two treatment groups in relation to child's classification (Table 2).

**Table II:** Child's classification of the patients of treatment.

| | Child's classification | | |
|---|---|---|---|
| | A | B | C |
| SMS 201-995 | 2 | 8 | 2 |
| Balloon tamponade | | | |
| Sum of the patients | 3 | 12 | 4 |

Furthermore, there were no significant differences in relation to the characteristics of the bleeding episode at the of admission in the Intensive Care Unit, prior to randomization. The interval between the time of admission and the initiation of drug infusion, the units of blood transfused during this interval, the hematocrit, the heart rate, the blood pressure, the number of patients with hypovolemic shock and the sites of bleeding were similar in the two groups.

SMS 201-995 infusion initially stopped the hemorrhage within first 4 h of treatment in 9 of the 12 patients treated (75%) and balloon tamponade in 5 of the 7 patients (71%) (not significant statistically) (Figure 1). Bleeding was controlled over a 48 h period 7 of the 12 patients treated

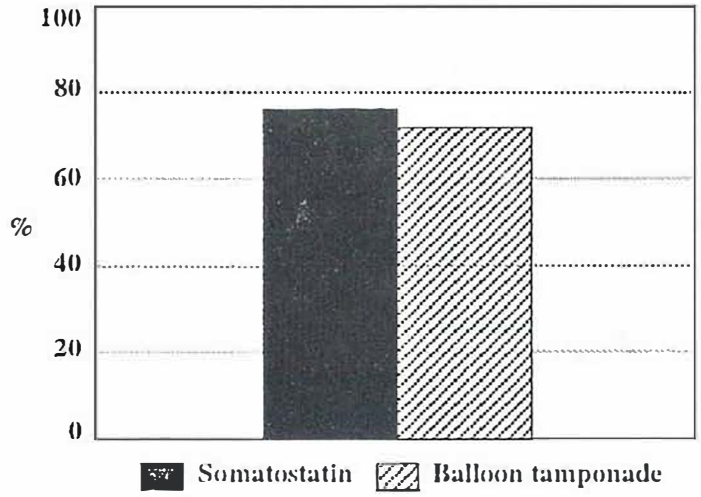


**Figure 1.** Primary haemostasia after the treatment.

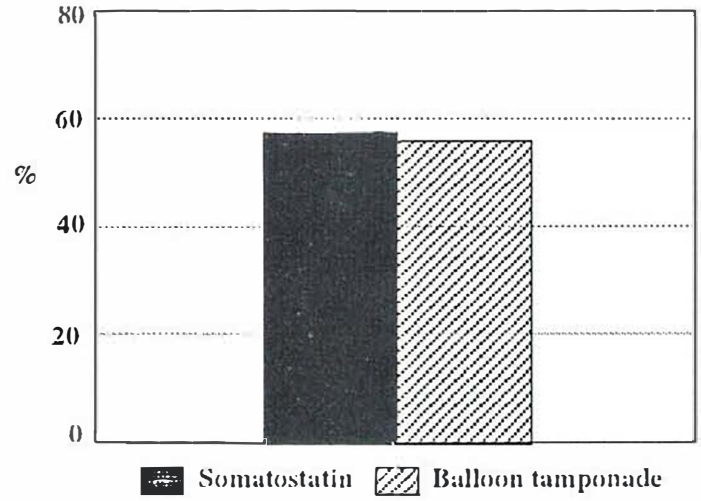


**Figure 2.** Bleeding over a 48 h period after the treatment.

(58%) in SMS group, and 5 of the 7 patients (57%) in balloon tamponade group (Figure 2).

Mortality during hospitalization was 2 patients in treatment balloon tamponade group. Two of the 7 patients treated with balloon tamponade died due to hepatic encephalopathy (Table 3, Figure 3).

The apparent similarity of the hemostatic efficacy of SMS 201-995 and balloon tamponade contrasts sharply with the marked differences observed in the complications associated with each therapy. Balloon tamponade produced a significantly higher number of complications than SMS 201-995.

**Table III:** Causes of death.

| | SMS 201-995 | Balloon Tamponade |
|---|---|---|
| Bleeding | 0 | 0 |
| Hepatic failure | 0 | 2 |
| Sum of the cases | 0 | 2 |

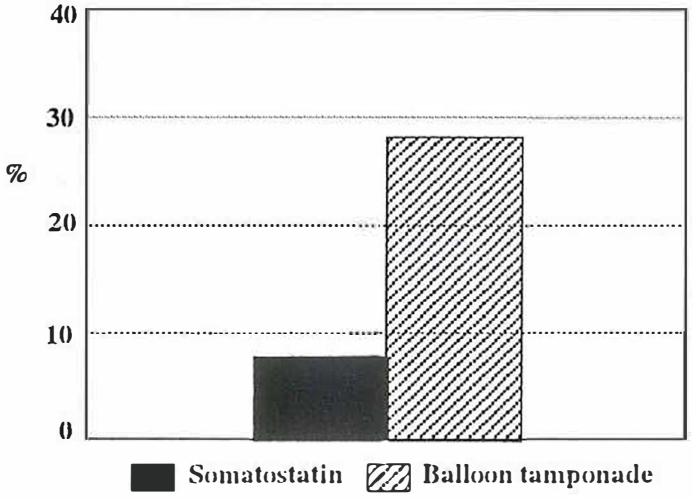


**Figure 3** Mortality after the treatment.

No difference in protrombin time jaundice, number of transfusion (figure 4) primer hemoestasis (Figure ), and rebleeding Figure 5 were found between the two groups. Rebleeding was 2 of the 9 patients (22.2%) treated with SMS 201-995 and 1 of 5 the patient (20%) treated with balloon tamponade (no sifnificant difference).

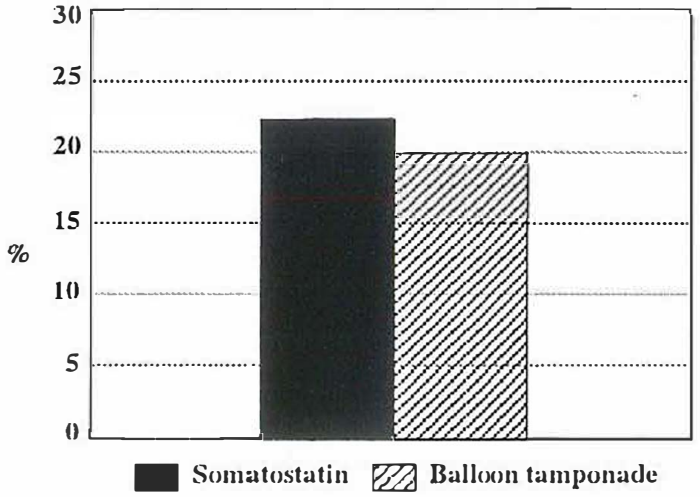


**Figure 5.** Rebleeding after the treatment.

## DISCUSSION

Variceal bleeding is known to stop spontaneously in 25-35% of cases (20,21). In the present study, primary haemostasia within the first 4 h of treatment was obtained 75% of the patients receiving SMS 201-995 and in 71.4% of these receiving Sengstaken balloon tamponade. The results confirmes that SMS 201-995 and balloon tamponade are equally effective in the treatment of variceal bleeding. Bot treatment achieved a hight rate of control of bleeding during the first hours of therapy.

SMS 201-995 is effective in controlling acute bleeding. Although it is good alternatives in the early management of bleeding, a 20-50% relapse rate has been reported following discontinuati-

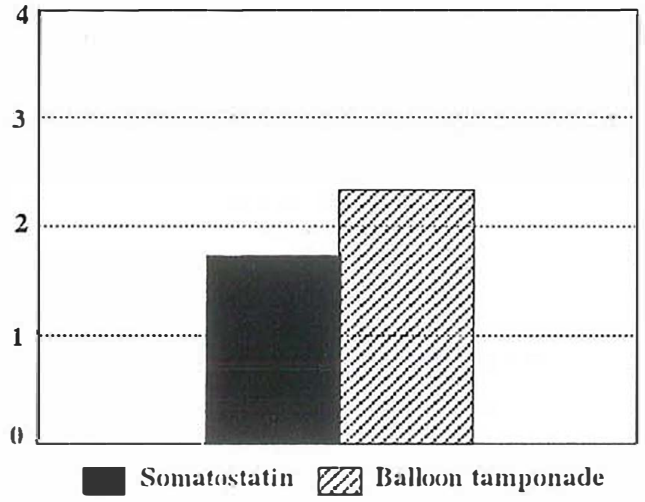


**Figure 4.** Transfusion number after the treatment.

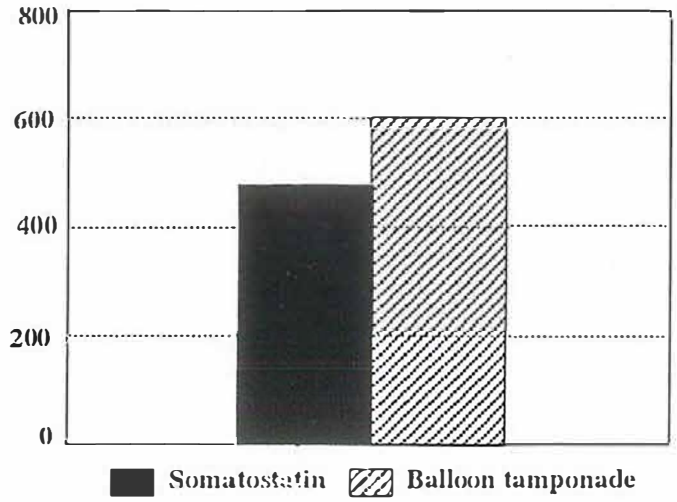


**Figure 6.** Cost of the each treatment.

on of treatment (10,17,22), strangly suggesting that they should only be used temporarily.

In this study initial haemostasia was obtained with SMS 201-995 infusion in 75% of the patients. These results are similar to other studies (16,17,18,23). No major complications due to SMS 201-995 were observed in our study. In a study a small proportion of patients, minor side effects (extrasystoles, diarrhoea) were observed (16).

In the present study, control of bleeding was obtained in 71% of patients bleeding from esophageal varices treated with the balloon tamponade 71.4% of the patients complained of chest pain, 1 of whom needed analgesia. Thus in general tolerance to tamponade was reosonably good. The major complication of balloon tamponade observed in a study was aspiration pneumonia, which appeared in 10% of the patients and in seven cases (4.6%) was probably a contributory factor to death (24). In other series the incidence of aspiration into the airways ranges from 0 to 21% (24-30). Our results clearly show that this complication is more frequent in patients with hepatic encephalopathy. Confirming the suggestion by studies, the study indicates that orotracheal intubation before passing the tube markedly reduces aspiration accidents (12,24) in patients with altered conciousness.

Although, recently, in our study, intravenous administration of SMS 201-995 markedly decreased portal flow in healthy human (9), the effects of SMS on portal hemodynamics remain controversial. Although most studies in animals (31-35) and humans (36-38) have found decreases in portal tributary blood flow or pressure others found no significant effect (4,39). SMS analogue is know to decrease levels of several vasodilatory hormones, including vasoactive intestinal polipeptide (VIP), pancreatic polipeptide (PP), and glucagon (40,41). Several humoral factors, in particular glucagon, may madiate chroni splanchnic hyperemia in portal hypertension (42). In rats with portal hypertension, SMS 201-995 had a vasoconstrictive effect as evidenced by the increase in arterial pressure and total peripheral resistance (35). Some evidence suggests that SMS 201-995 also has a direct vasoconstrictive action (33,37).

From the literature (17,18,20) and the present study it can be concluded that SMS 201-995 is an effective drug for the management of variceal bleeding. Its efficacy is comparable to balloon tamponade appear to be similar. In addition, it is safer and entails a lower risk of side effects and complications than balloon tamponade. Thus, although larger studies are necessary, we belive that, SMS 201-995 can be considered as a primary treatment choice for causes of acute variceal bleeding. Also, other advantage of SMS 201-995 is its log cost (Figure 6), because being expensive Sengstaken-Blakemore tube than SMS.

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