0002-9270/95/9011-1923$03.00/0
THE AMERICAN JOURNAL OF GASTROENTEROLOGY Vol. 90, No. 11, 1995

Clinical review

Nonsurgical Treatment of Variceal Bleeding: New Modalities

Kenneth F. Binmoeller, M.D., and Nib Soehendra, M.D.

Department of Endoscopic Surgery, University Hospital Eppendorf Hamburg, Germany

INTRODUCTION

Endoscopic sclerotherapy (ES) is widely accepted as the treatment of choice for bleeding esophageal varices. Randomized, controlled studies have shown sclerotherapy to be superior to medical treatment in the control of active bleeding and long-term prevention of rebleeding (1). Nevertheless, the results of sclerotherapy have not been ideal. Acute esophageal variceal bleeding may be refractory to sclerotherapy in up to one-third of patients, and rebleeding may occur in up to 50% of patients (2-8). Sclerotherapy has been associated with a host of complications, of which some have resulted in substantial morbidity and mortality (9, 10). Gastric variceal bleeding poses a special problem; study protocols evaluating sclerotherapy have generally excluded gastric variceal bleeding because of notoriously poor rates of response to sclerotherapy (11, 12).

The above shortcomings of sclerotherapy have fostered the development of new nonsurgical modalities to treat bleeding varices. These include the endoscopic modalities variceal ligation and cyanoacrylate injection, the transjugular intrahepatic portosystemic shunt (TIPS), and drug therapy with glypressin, somatostatin, or octreotide. The current status of these new nonsurgical treatments will be reviewed.

ENDOSCOPIC VARICEAL LIGATION

Endoscopic variceal ligation (EVL) was introduced in 1986 by Stiegmann *et al.* (13). Inspired by the technique of band ligation for hemorrhoids, EVL consists of ensnaring esophageal varices with elastic bands (Fig. 1). The varix is first aspirated into a hollow cylinder attached to the tip of the endoscope. An elastic band, mounted on the distal end of the cylinder, is then released over the varix by pulling on a trip wire that runs through the working channel of the endoscope. The strangulated varix thrombosis and the tissue sloughs over 3-5 days, leaving a shallow ulcer that heals over the course of 2-3 wk.

Five controlled trials comparing ES with EVL have been published to date (14-18) (Table 1). The results have shown that EVL and ES have comparable efficacy in controlling active variceal bleeding and eradicating varices. However, EVL consistently achieved eradication more quickly and with fewer complications than ES. These advantages probably contributed to a significantly lower rebleeding rate in the trial by Gimson *et al.* (15), and a trend toward lower rebleeding in the trials by Stiegmann *et al.* (14) and Laine *et al.* (19). Survival in EVL-treated patients was found to be significantly improved in one trial (14). A meta-analysis of randomized clinical trials of patients presenting with esophageal bleeding revealed EVL to reduce significantly the number of treatment sessions to achieve eradication, rebleeding episodes, and local nonbleeding complications (16).

The lower complication rates after EVL, compared with ES, can be explained by inherent differences in the potential of these techniques for inducing tissue injury. With EVL, the extent and depth of tissue injury is largely limited by the instrument itself; only the mucosal and submucosal layers are aspirated into the cylinder attachment. Microscopic examination of EVL-treated sites in animal and postmortem studies have shown the depth of inflammation and scarring to be confined to the submucosal layer of the esophageal wall (20, 21). In contrast, sclerotherapy can induce variable degrees of tissue injury, depending on the sclerosant used, concentration and amount of sclerosant injected, and technique of injection. Some studies have demonstrated severe transmural inflammation and necrosis following sclerotherapy (22).

In the controlled trial by Young *et al.* (18), ulcers produced by ES and EVL were compared by means of a scored ERCP cannula to measure length, width, and depth. Sclerotherapy was performed with 1.5% sodium tetradecyl sulfate injected intravariceally. ES ulcers were found to be consistently deeper and took significantly longer to heal (20.9 days vs. 14.4 days). None of the patients in the EVL group, compared with two patients in the ES group, developed esophageal strictures.

Serious life-threatening complications after EVL are rare.

Received Jan. 25, 1995; accepted June 14, 1995.

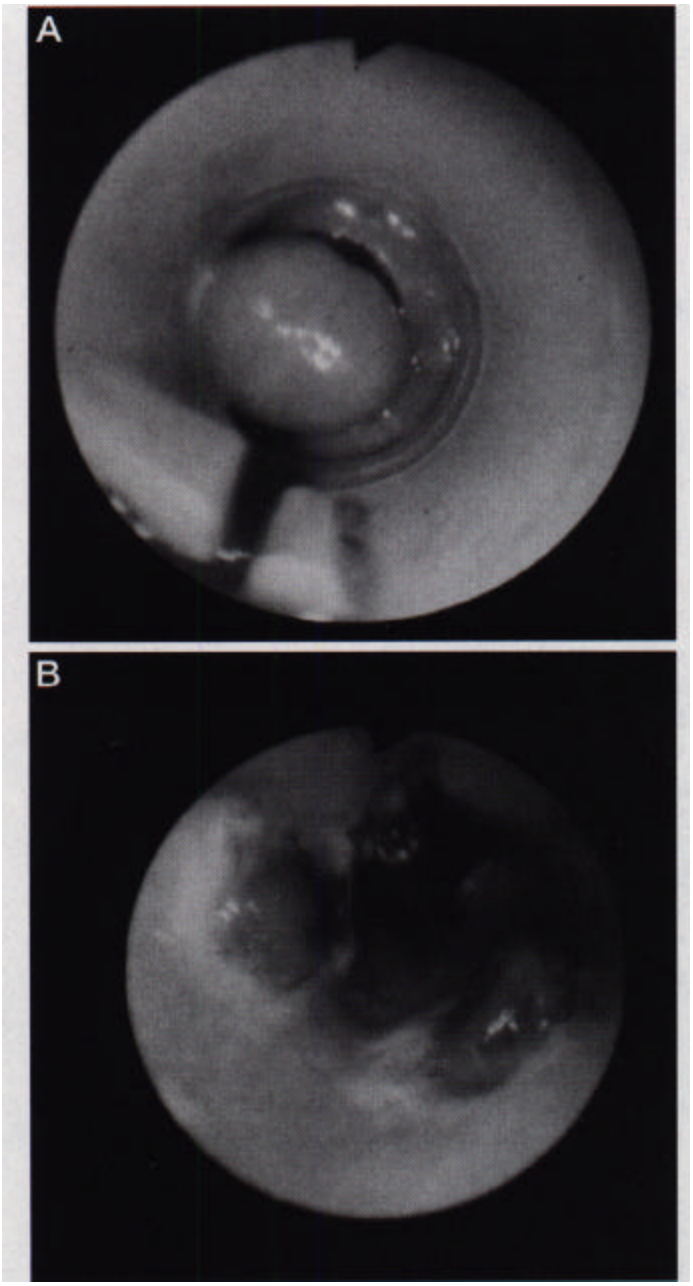


FIG. 1. Endoscopic variceal ligation (EVL). A, endoscopic view of an esophageal varix immediately after EVL. The cylinder attachment at the tip of the endoscope reduces the field of vision by approximately one-third. B, follow-up endoscopy 1 wk later showing necrosis and sloughing of varices.

Most reported complications have been related to the use of the overtube, which allows easy passage of the endoscopic ligating device through the hypopharynx. There have been several reports of severe bleeding and perforation (23-28), presumably caused by pinching of the esophageal wall in the gap between the overtube and the endoscope. Insertion of the overtube over an appropriately sized bougie as an obturator has been recommended to minimize this risk (23). Massive bleeding was reported distal to the overtube, probably due to blockage of venous outflow by the overtube (29). In another case, acute esophageal obstruction resulted from lumen obstruction by banded varices (29). Distal esophageal spasm induced by ligation may also contribute to obstruction. EVL-induced ulcers are usually shallow but occasionally acquire significant depth and result in severe bleeding (24). Severe early rebleeding after EVL of esophageal varices in patients with Child-Pugh class C cirrhosis has been reported by Sakai *et al.*, leading these authors to question whether EVL is contraindicated in this patient subgroup (30).

EVL may have economic advantages over ES. The procedural costs were evaluated by the ASGE Technology Assessment Committee and were found to be roughly equivalent to that of sclerotherapy (31). If one takes into consideration that EVL requires fewer sessions to achieve eradication, EVL is probably less costly. A lower complication rate should also contribute to a reduction in overall health care cost.

If EVL can achieve results that are at least as good as sclerotherapy, with fewer complications and lower cost, should it not replace sclerotherapy? The answer was affirmative in a recent international consensus conference on portal hypertension (32). However, it would be premature to abandon sclerotherapy altogether. Some varices may be better suited for treatment by sclerotherapy. In our experience, previously treated varices embedded in a nonpliable mucosa are difficult to aspirate into the cylinder attachment and therefore cannot be adequately treated with EVL.

The combination of EVL with sclerotherapy, either synchronously or metachronously, may produce results superior to those obtainable with either treatment alone. In the controlled trial by Hashizume *et al.* (17), patients with bleeding esophageal varices were randomized to EVL or ES in the initial session, followed by ES for all subsequent sessions. Patients undergoing combined therapy required significantly fewer sessions to achieve complete eradication and less total volume of sclerosant. Complications such as fever, retrosternal pain, and pleural effusion were significantly lower in the combined EVL and ES group.

Several technical drawbacks of EVL deserve mention. The endoscope must be removed from the esophagus for band reloading each time a band is applied. Reloading prolongs the procedure, which may be critical in the actively bleeding or uncooperative patient. The endoscopic field of vision is reduced by approximately 30% due to the cylinder attachment at the end of the endoscope. The cylinder also has the disadvantage that it impedes selective aspiration of blood or secretions, since the area of suction is expanded to the cylinder circumference. These shortcomings are likely to be overcome with future technical improvements. A new band ligator capable of applying multiple bands is currently undergoing investigation. Initial experience with a transparent ligation device has been reported to provide an improved field of view (33).

Preliminary data in abstract form suggest that EVL can be used for the treatment of gastric varices (34). However, large fundal varices are likely to be problematic, because

TABLE 1
Controlled Studies of Endoscopic Variceal Ligation

	Therapy	No. of Patients	Active Bleeding (%)	Initial Hemostasis (%)	Eradication Sessionsa %	Mean	Rebled (%)	Complications (%)	Survival (%)
Stiegmann *et al. (14)*	ES	*65*	*20*	*77*	*56*	*5*	*48*	*22t*	*55t*
	EVL	*64*	*22*	*86*	*55*	*4*	*36*	*2t*	*72t*
Gimson *et al. (15)*	ES	*49*	*47*	*92*	*55*	*4.9t*	*53t*	*8*	*52*
	EVL	*54*	*39*	*91*	*59*	*3.4t*	*30t*	*2*	*37*
Laine *et al. (16)*	ES	*39*	*23*	*89*	*69*	*6.2t*	*44*	*56t*	*77*
	EVL	*38*	*24*	*89*	*59*	*4.1t*	*26*	*24t*	*81*
Hashizume *et al. (17)*	ES	*25*	*0*	NA	100	*4*	ND	§	ND
	EVL + ES	*25*	*0*	NA	100	*3.6*	ND	§	ND
Young *et al. (18)*	ES	*13*	*0*	NA	*85*	*6.2t*	ND	*15*	*92*
	EVL	*12*	*0*	NA	*90*	*3.OtN*	ND	0	*90*

ND, no data; NA, not applicable.
* Sessions to achieve eradication of varices.
j- p < 0.05.
§ Significantly fewer patients developed fever, chest pain, pleural effusions, and ulcers in the combined EVL and ES group.

only a portion of the varix is ligatable. A major concern is the possibility of massive early rebleeding at the necrosis site (35). Junctional varices that extend below the cardia are probably good candidates for EVL.

A modification of the variceal ligation technique was reported by Yoshida *et al.* (36), who used a detachable snare. The snare opens to a diameter of 4 cm and is therefore better suited for the treatment of large varices. Ligation of gastric varices was performed electively in nine patients and emergently for active bleeding in one patient. There was no rebleeding during short-term follow-up. Further trials with this new device are required before this technique can be recommended.

CYANOACRYLATE INJECTION

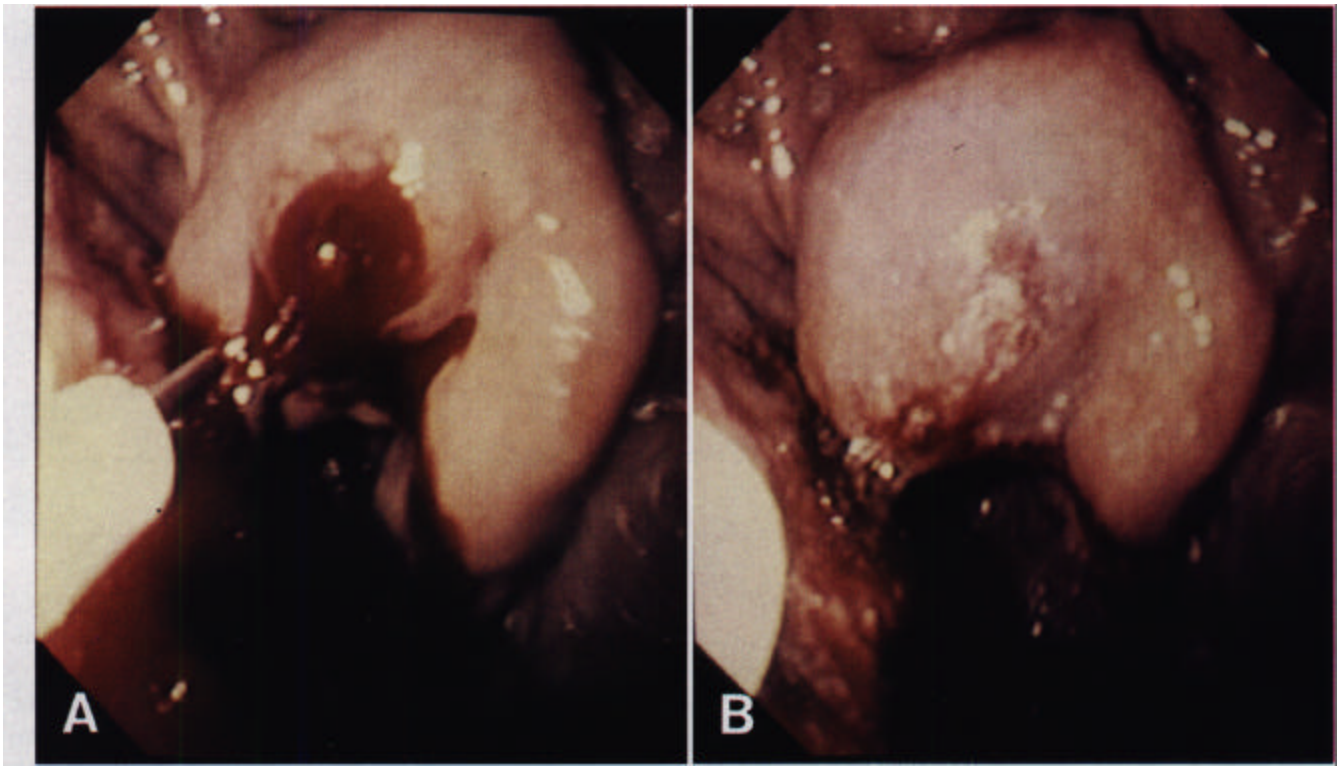
The cyanoacrylate tissue adhesive Histoacryl (N-butyl-2-cyanoacrylate) is a remarkable substance that transforms from its native liquid to a solid state when added to a physiological medium such as blood. When instilled into a varix by the standard method of intravariceal injection, Histoacryl undergoes an instantaneous polymerization reaction and hardens, thereby plugging the varix lumen. This enables rapid hemostasis of an actively bleeding varix (Fig. 2). Total lumen occlusion with the cyanoacrylate prevents rebleeding of the treated varix.

The first reports of the use of cyanoacrylates for the endoscopic treatment of variceal bleeding were from France (37) and Germany (38) a decade ago. More recently, studies from other countries have appeared (39-43) (Table 2). Most studies have reported control of active variceal bleeding in 100% of patients. Rebleeding rates were found to be high in studies that evaluated the use of cyanoacrylates as sole therapy for variceal bleeding (37, 44-46). Hence, cyanoacrylate injection has been combined with conventional sclerotherapy, the latter aimed at the eradication of smaller esophageal varices that cannot be adequately treated by cyanoacrylate injection. With the combined treatment, rebleeding rates in the order of 10% have been reported.

Recently Thakeb *et al.* (43) from Egypt reported the results of a randomized, controlled trial comparing a combination of Histoacryl and sclerotherapy with 5% ethanolamine oleate to sclerotherapy alone for the treatment of esophageal and gastric varices. Immediate hemostasis rates were similar (100% and 96% for the Histoacryl and sclerotherapy groups, respectively), but patients undergoing combined treatment had a significantly lower rebleeding rate (9% vs. 25%). There was no significant difference in overall mortality between the two groups; however, the causes of death were strikingly different. Liver failure was the major cause of death in the combined group (only one patient died of bleeding), whereas bleeding was the major cause of death in the sclerotherapy group.

Intravariceal injection of cyanoacrylates appears to be safe. In a review of 317 patients treated with bucrylate or Histoacryl over a 5-yr period, Gotlib (46) reported no procedure-related mortality and only minor complications, including dysphagia with and without stenosis, bacteremia, and pyrexia. We have treated more than 400 patients with bleeding esophageal and gastric varices using Histoacryl injection, without any major complications. Nonetheless, serious complications associated with postinjection embolization of cyanoacrylate have been reported in isolated cases. Cerebral stroke, presumably due to anomalous right to left shunting, was reported in two cases (47), and there was a report of pulmonary (40) and portal vein (43) embolism. Limiting injection aliquots of the cyanoacrylate to a maximum of 1 ml has been recommended to prevent this potential complication (48).

The issue of potential carcinogenicity of cyanoacrylates was raised by an experimental study in which the cyanoacrylate bucrylate (isobutyl-2- cyanoacrylate)-induced sarcomas after implantation into the rat peritoneum (49). How-



Ft- 2. Endoscopic cyanoacrylate (Histoacryl) injection. A, endoscopic view of a bleeding fundal varix prior to cyanoacrylate injection. *B*, plugging of the varix and hemostasis following a single injection of Histoacryl (1.0 ml).

TABLE 2
Results of Cyanoacrylate Injection for Variceal Bleeding

	Treatment	No. of Patients	Active Bleeding [n (%)]	Hemostasis	Rebleeding (Follow-up)
Gotlib, 1984 (37)	Cyanoacrylate alone	96	21 (22%)	95%	36% (9 mo)
Ramond, 1986 (44)	Cyanoacrylate alone	49	15 (31%)	93%	42%0 (1 yr)
Ramond, 1989 (45)	Cyanoacrylate alone	27	6 (22%)	100%	37% (14.7 mo)
Gotlib, 1990 (46)	Cyanoacrylate alone	317	120 (38%)	ND	20% (1 mo)
Mostafa, 1993 (40*)	Combined	100	100 (100%)	100%	10%
Feretis, 1990 (39)	Combined	23	18 (78%)	96%	4% (2.4 mo)
Pretis, 1993 (41*)	Combined	29	18 (62%)	100%	6.1%
Dal Monte, 1994 (42*)	Combined	71	36(51%)	94%	10.6%
Thakeb, 1995 (43)	Combined	58	ND	100%	8.6%0
Own Series	Combined	407	258 (63%)	100%	10.1%

ND, no data. Combined, cyanoacrylate and sclerotherapy.
* Abstract form only.

ever, this study has been criticized because the rat species selected had a known predisposition to sarcoma formation, there was no control group, and the doses used was 100 times higher than those used in humans (50). Further studies are therefore needed before carcinogenicity can be viewed as established. Cyanoacrylates have been applied as a tissue adhesive, embolization agent, and hemostatic agent in various medical specialities over the past 3 decades (51-53), and there have been no reports of carcinogenicity. Furthermore, the risk of carcinogenicity following intravariceal injection should be negligible, because radiographic studies have shown that the cyanoacrylate is expelled from the varix lumen over a period of weeks (Fig. 3).

Although the basic technique of cyanoacrylate injection is similar to that of intravariceal sclerotherapy, unique properties of the cyanoacrylates make some modifications necessary. Histoacryl should be diluted with the oily contrast agent Lipiodol to prevent premature solidification within or at the tip of the injection catheter during injection. Using a dilution ratio of 0.5 ml Histoacryl to 0.8 cc Lipiodol, hardening is delayed by approximately 20 s (54). The injection catheter is "prepped" by injecting several milliliters of Lipiodol into the catheter, followed by a syringe-full of air; this coats the inner wall of the catheter and prevents Histoacryl from sticking to the catheter. To ensure that the total volume of Histoacryl injected (0.5 ml for esophageal and 1.0

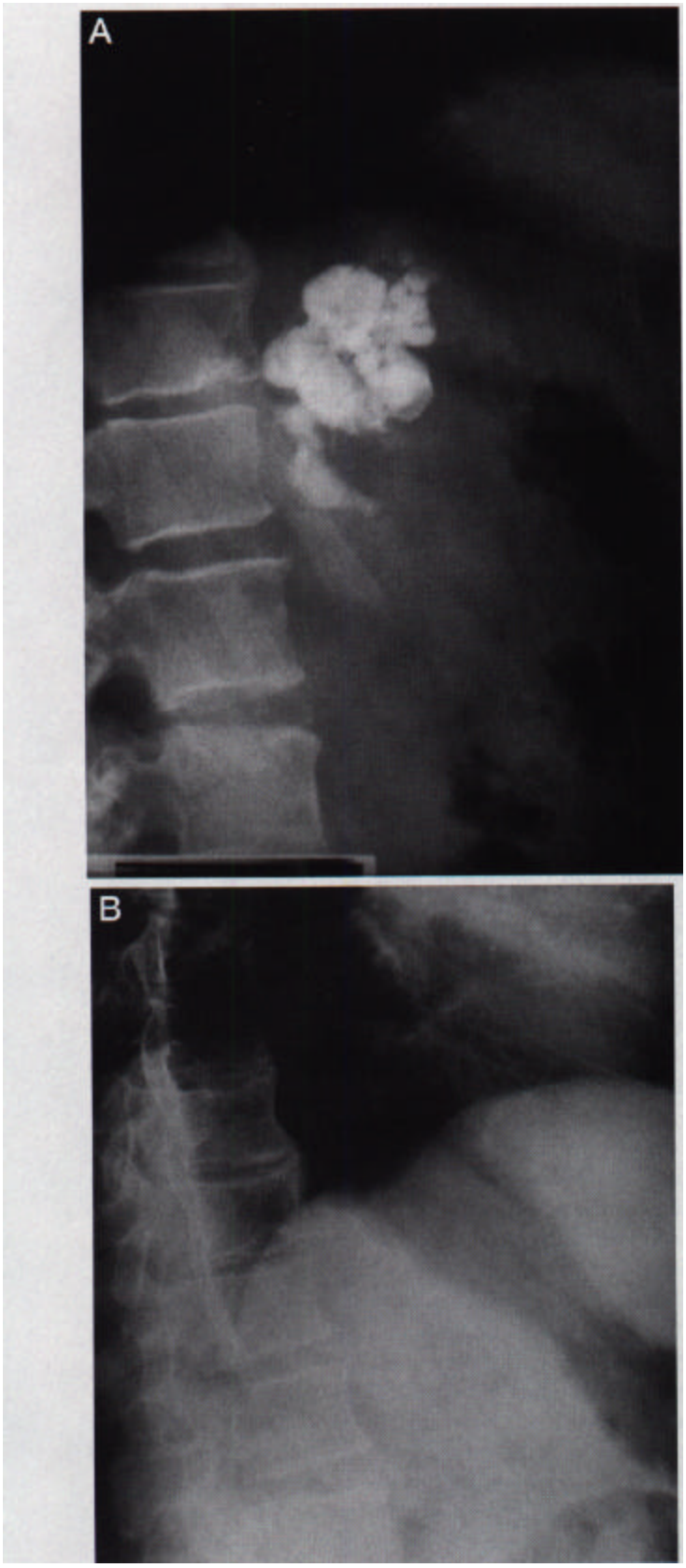


FIG. 3. A, radiograph showing fundal varices filled with a mixture of Histoacryl and the contrast medium Lipiodol. B, same patient 6 months later showing disappearance of the Histoacryl-Lipiodol mixture. Variceal eradication was confirmed endoscopically.

ml for gastric varices) is actually deposited in the varix, it is necessary to follow the Histoacryl injection with a second injection of distilled water. The volume injected should be equal to the dead space of the catheter (approximately 1 ml).

In summary, there is accumulating evidence that cyanoacrylate injection can significantly improve the results of sclerotherapy. The major advantages of this technique are the ability to control active variceal bleeding rapidly and to treat gastric varices effectively. The technique should be viewed as complementary rather than competitive with conventional sclerotherapy.

TIPS

TIPS is the construction of a portosystemic shunt by transjugular insertion of an expandable metallic stmt between the hepatic and portal veins under radiological guidance. It has the advantage of being less invasive than the surgical shunt. Early experience with TIPS showed encouraging results (55-57). The technical success rate was over 90%, and portal pressure reduction of up to 50% of the preprocedural levels was achieved. However, initial enthusiasm has been tempered by more recent studies that highlight two significant postshunt problems: hepatic encephalopathy and stem stenosis or occlusion.

Expandable metallic stems used to create a TIPS have a propensity to obstruct over time. The rates of shunt stenoses or occlusions have been variable in larger series, ranging from 16% to 50% (58-62) (Table 3). This variation has been due in part to different criteria for defining stenosis, study protocols, follow-up periods, and percentages of patients who underwent liver transplantation after TIPS. Early stenosis appears to be more common than was initially appreciated. Stenosis is primarily due to pseudointimal hyperplasia. In one study, shunts occluded by pseudointimal hyperplasia or thrombosis in 59% of cases during 6-month follow-up (63). Approximately 50% of stems will require revision to reestablish patency at 1 yr (62, 64). Early follow-up to detect and promptly revise occluded shunts is recommended.

Hepatic encephalopathy is a familiar problem after surgical shunt therapy and is probably a necessary trade-off of an effective shunt. The prevalence of encephalopathy has been reported to occur in 20-30% of cases (60, 65-67), which is comparable to that among patients with surgical shunts. Hepatic encephalopathy has not been found to correlate with Child-Pugh class, suggesting that factors other than hepatic function play a pathogenetic role. Progressive narrowing of the stem due to intimal hyperplasia may explain a decline in the incidence of hepatic encephalopathy after an initial peak several months after placement (60).

A number of miscellaneous complications have been reported in association with TIPS placement. These included procedural complications such as liver capsule perforation, intraperitoneal hemorrhage, and hemobilia, and stmt-in-

TABLE 3
Results of TIPS for Variceal Bleeding

	No. of Patients	Stent Type	Technical Success	Stenosis/ Occlusion	Rebleeding	Encephalopathy	Follow-up
Simpson, 1993 (58)	22	Palmaz	81%	39%	56%	11%	1-15 mo
LaBerge, 1993 (559	100	Wallstent	96%	16%	19%	18%	4.7 mo (mean)
Rossle, 1994 (60)	100	Palmaz	93%	33%	11%	25%	12 mo (mean)
Haskal, 1994 (61)	100	Wallstent	NA	50%	ND	ND	11 mo (mean)
Nazarian, 1994 (62)	24	Wallstent	NA	37%	6%	ND	6 mo (mean)

NA, not applicable; ND, no data.

duced complications such as pulmonary embolization and portal vein thrombosis. Complications of a systemic nature included kidney failure, septic shock, and intravascular hemolysis (68).

TIPS, which is significantly less invasive than shunt surgery, undoubtedly offers an attractive alternative to sclerotherapy in the management of variceal bleeding. It has gained popularity as a "bridge" to liver transplantation because of its beneficial effects on ascites, renal function, and nutritional status (58, 69, 70). However, controlled trials comparing TIPS with sclerotherapy should be awaited before TIPS can be recommended as first-line therapy. Rigorous evaluation of the problem of stenosis or occlusion in long-term follow-up studies, with the attendant risk of rebleeding, will be necessary. If close surveillance and frequent stent exchanges are necessary, the issue of cost deserves consideration, as there are substantial procedural charges (71). Finally, the role of emergency TIPS in the setting of active variceal bleeding will need to be defined. A recent report of a mortality rate of 56% for emergent TIPS, versus 5.5% for nonemergent TIPS (71), suggests that variceal hemorrhage should be arrested by other modalities prior to TIPS.

NEW DRUGS

Pharmacological treatment can be used as a temporizing measure to stop or reduce variceal bleeding pending more definitive treatment. Drug therapy has inherent advantages, because it is readily available and does not require sophisticated equipment or specialized training.

Vasopressin, which reduces blood flow and pressure within esophageal varices, has been the standard treatment in many medical centers. However, the therapeutic efficacy of vasopressin in controlling variceal bleeding has not been proven (72). The most recent randomized controlled trial comparing intravenous vasopressin to placebo found no benefit in terms of hemostasis (29% vs. 37%, respectively) or mortality (73). Of two studies that compared vasopressin to balloon tamponade, vasopressin was as effective in one study (74) but was inferior in the other (75). The significant drawback of vasopressin is its hemodynamic side effects due to vasconstriction of systemic regional circuits. Myocardial infarction, skin gangrene, and bowel gangrene all have been reported. Nitroglycerin vasodilators were found to reduce the systemic side-effects of vasopressin in three controlled trials and, therefore, should be combined with vasopressin if this drug is used (76-78).

Newer vasoactive drugs may improve our ability to control acute variceal bleeding. Glypressin is a synthetic analogue of vasopressin that appears to have a better therapeutic index and fewer side effects than vasopressin. In contrast to vasopressin, which requires continuous intravenous infusion because of a short half-life, glypressin can be administered by bolus intravenous injections. Of three published controlled trials comparing glypressin to placebo, all showed a significant reduction in bleeding and one showed a significant reduction in mortality (79). Glypressin was effective as balloon tamponade in one study (74). Glypressin has been reported to have fewer adverse systemic effects than vasopressin alone (80) and to vasopressin combined with nitroglycerin (81). It is unclear whether the addition of nitroglycerin improves the safety profile of glypressin.

Somatostatin and its long-acting analogue, octreotide, reduce splanchnic blood flow and cause a significant decrease in variceal pressure, but without inducing changes in the systemic vascular system (82). Hence, hemodynamic side effects are virtually absent, making these drugs safe for treatment in the emergency room or even out in the field. Two of three uncontrolled studies of somatostatin therapy have shown benefit for variceal bleeding (83, 84), and randomized studies have shown somatostatin or octreotide to be as effective (85-87) or more effective than vasopressin (88-91) and as effective as balloon tamponade (92) or sclerotherapy (93). However, two recent placebo-controlled trials have shown conflicting results. A British study from the Royal Free Hospital (94) showed somatostatin to be significantly more effective than placebo, whereas a multicenter trial in the United States (95) showed intravenous somatostatin to be no more effective than placebo in the control of active variceal bleeding. Both studies did, however, show similar hemostasis rates for somatostatin (64% and 65%). An unusually high placebo response rate of 83% in the American study suggests that patient selection may have accounted for an absence of benefit for somatostatin. Further controlled clinical trials are clearly warranted to resolve this confusion in the literature.

NEW MODALITIES IN PERSPECTIVE

On the basis of the available data, we propose the following preliminary guidelines regarding the use of the new modalities in the management of variceal bleeding. Endoscopic treatment remains the approach of choice and should be carried out at the time of diagnostic endoscopy. Cyanoacrylate injection is best suited for the treatment of actively bleeding varices and gastric varices. EVL is the next best alternative to cyanoacrylate injection for the treatment of actively bleeding varices, and is the modality of choice for the elective treatment for esophageal varices. Sclerotherapy is still indicated for varices that cannot be adequately treated by EVL. TIPS should be generally reserved for patients who fail endoscopic treatment but deserves consideration as firstline treatment for fundal varices if cyanoacrylate injection is not available, in the patient with concomitant "difficult" ascites, or the patient awaiting liver transplanation. Vasoactive drugs have become more effective and safer, and they play an important role in the acute management of variceal bleeding when emergency endoscopic treatment is not available. The newer vasoactive drugs (glypressin, somatostatin, octreotide) are safer and probably more effective than vasopressin. Like balloon tamponade, drug therapy should be viewed as a temporizing measure to tide the patient over until endoscopic treatment is available. Because balloon tamponade is more invasive than drug therapy and can result in significant complications *(e.g.,* esophageal rupture, aspiration), it should be reserved as a last resort measure in the patient who threatens to exsanguinate from variceal bleeding.

CONCLUSION

Endoscopic sclerotherapy is widely accepted as the procedure of choice for the management of bleeding esophageal varices. However, results have not been ideal, and significant limitations have been recognized. New nonsurgical treatment modalities have thus emerged and are undergoing evaluation. Each of the new modalities discussed in this review have shown favorable results and can contribute to the successful management of variceal bleeding. The task of future studies will be to define the optimal approach for different patient subgroups. Despite these advances, we should not forget to consider the suitability and timing of hepatic transplantation after bleeding has been controlled.

Reprint requests and correspondence: Kenneth F. Binmoeller, M.D., Department of Endoscopic Surgery, University Hospital Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.

REFERENCES

1. Infante RC, Esnaola S, Villeneuve JP. Role of endoscopic variceal sclerotherapy in the long-term management of variceal bleeding: A meta-analysis. Gastroenterology 1989;96:1087-92.
2. Terblanche J, Yakoob HI, Bornman PC, et al. Acute bleeding varices: A five-year prospective evaluation of tamponade and sclerotherapy. Ann Surg 1981;194:521-30.
3. Barsoum MS, Bolous FI, El RA, et al. Tamponade and injection sclerotherapy in the management of bleeding oesophageal varices. Br J Surg 1982;69:76-8.
4. Soderlund C. Copenhagen Esophageal Varices Sclerotherapy Project. Sclerotherapy after first variceal hemorrhage in cirrhosis. N Engl J Med 1984;311:1594-600.
5. Larson AW, Cohen H, Zweiban B, et al. Acute esophageal variceal sclerotherapy. Results of a prospective randomized controlled trial. J Am Med Assoc 1986;255:497-500.
6. Soderlund C, Ihre T. Endoscopic sclerotherapy v. conservative management of bleeding oesophageal varices. A 5-year prospective controlled trial of emergency and long-term treatment. Acta Chir Scand 1985;151:449-56.
7. Korula J, Balart LA, Radvan G, et al. A prospective, randomized controlled trial of chronic esophageal variceal sclerotherapy. Hepatology 1985;5:584-9.
8. Westaby D, Hayes PC, Gimson A, et al. Controlled clinical trial of injection sclerotherapy for active variceal bleeding. Hepatology 1989; 9:274-7.
9. Sanowski RA, Waring JP. Endoscopic techniques and complications in variceal sclerotherapy. J Clin Gastroenterol 1988;10:504-13.
10. Zambelli A, Pisano G, de Grazia F, et al. Complications of the endoscopic sclerotherapy of esophageal varices. G Ital Endosc Dig 1991;14:103-19.
11. Trudeau W, Prindiville T. Endoscopic injection sclerosis in bleeding gastric varices. Gastrointest Endosc 1986;32:264-8.
12. Yassin MY, Eita MS, Hussein AMT. Endoscopic sclerotherapy for bleeding gastric varices. Gut 1985;26:A1105.
13. Stiegmann GV, Cambre T, Sun JH. A new endoscopic elastic band ligating device. Gastrointest Endosc 1986;32:230-3.
14. Stiegmann GV, Goff JS, Michaletz OP, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med 1992;326:1527-32.
15. Gimson A, Ramage JK, Panos MZ, et al. Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. Lancet 1993;342:391-4.
16. Lame L, Cook D. Endoscopic ligation vs sclerotherapy for esophageal variceal bleeding: A meta-analysis. 1994;40(part 2):A77.
17. Hashizume M, Ohta M, Ueno K, et al. Endoscopic ligation of esophageal varices compared with injection sclerotherapy: A prospective randomized trial. Gastrointest Endosc 1993;39:123-6.
18. Young MF, Sanowski RA, Rasche R. Comparison and characterization of ulcerations induced by endoscopic ligation of esophageal varices versus endoscopic sclerotherapy. Gastrointest Endosc 1993;39:11922.
19. Laine L, El NH, Migikovsky B, et al. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. Ann Intern Med 1993;119:1-7.
20. Stiegmann GV, Sun JH, Hammond WS. Results of experimental endoscopic esophageal varix ligation. Am Surg 1988;54:105-8.
21. Marks RD, Arnold MD, Baron TH. Gross and microscopic findings in the human esophagus after esophageal variceal band ligation: A postmortem analysis. Am J Gastroenterol 1993;88:272-4.
22. Evans DM, Jones DB, Cleary BK, et al. Oesophageal varices treated by sclerotherapy: A histopathological study. Gut 1982;23:615-20.
23. Goldschmiedt M, Haber G, Kandel G, et al. A safety maneuver for placing overtubes during endoscopic variceal ligation. Gastrointest Endosc 1992;38:399-400.
24. Johnson PA, Campbell DR, Antonson CW, et al. Complications associated with endoscopic band ligation of esophageal varices. Gastrointest Endosc 1993;39:181-5.
25. Berkelhammer C, Madhav G, Lyon S, et al. "Pinch" injury during overtube placement in upper endoscopy. Gastrointest Endosc 1993;39: 186-8.
26. Golkel H Frohlich E. A severe complication of endoscopic band ligation of esophageal varices. Leber Magen Darm 1994;24:77-8.
27. El NH, Mihas AA. Esophageal perforation as a complication of endoscopic overtube insertion. Am J Gastroenterol 1994;89:953-4.
28. Minoli G. Esophageal perforation and variceal banding. Endoscopy 1994;26:7.
29. Saltzman JR, Arora S. Complications of esophageal variceal band ligation. Gastrointest Endosc 1993;39:185-6.

30. Sakai P, Malaf FF, Melo JM, et al. Is endoscopic band ligation of esophageal varices contraindicated in Child-Pugh C patients? Endoscopy 1994;26:511-2.
31. Gilbert DA. ASGE Technology Assessment Committee. Endoscopic band ligation of varices. Gastrointest Endosc 1993;39:670-2.
32. De Franchis R, et al. Baveno Il, 2nd International Consensus Workshop: Definitions, methodology and therapeutic strategies in portal hypertension. Baveno, April 1995.
33. Hashizume M, Ohta M, Ueno K, et al. A transparent endoscopic elastic band ligating device. Gastrointest Endosc 1993;39:686-8.
34. Khandelwal M, Jones WF, Akerman P, et al. Preliminary results of a prospective randomized trial of Histoacryl vs endoscopic band ligation for acute esophago-gastric variceal hemorrhage. Gastrointest Endosc 1994;40(part 2):A76.
35. Stiegmann GV. Elastic band ligation of esophageal and gastic varices. In: Barkin JS, O'Phelan CA, eds. Advanced therapeutic endoscopy. New York: Raven Press, 1994:95-103.
36. Yoshida T, Hayashi N, Suzumi N, et al. Endoscopic ligation of gastric varices using a detachable snare. Endoscopy 1994;26:502-5.
37. Gotlib JP, Zimmermann P. Une nouvelle technique de traitement endoscopique des varices oesophagiennes: 1'obliteration. Endosc Dig 1984;7:10-2.
38. Soehendra N, Nam V, Grimm H, et al. Endoscopic obliteration of large esophagogastric varices with bucrylate. Endoscopy 1986;18:25-6.
39. Feretis C, Tabakopoulos D, Benakis P, et al. Endoscopic hemostasis of esophageal and gastric variceal bleeding with Histoacryl. Endoscopy 1990;22:282-4.
40. Moustafa 1, Omar MM, Nooh A. Endoscopic control of gastric variceal bleeding with butyl cyanoacrylate. Endoscopy 1993;25:All.
41. Pretis G, De CM, Guelmi A, et al. N-Butyl-cyanoacrylate in bleeding oesophageal and gastric varices: Experience in 135 cirrhotic patients. Endoscopy 1993;25:A5.
42. Dal Monte PP, Baroncini D, Piemontese A, et al. N-Butyl-2-cyanoacrylate in the endoscopic treatment of upper GI varices. Endoscopy 1994;26:A401.
43. Thakeb F, Kader S, Salama Z, et al. The value of the combined use of N-butyl-2-cyanoacrylate and ethanolamine oleate in the management of bleeding esophagogastric varices. Endoscopy 1993;25:A5.
44. Ramond MJ, Valla D, Gotlib JP, et al. Endoscopic obliteration of esophagogastric varices with bucrylate. I. Clinical study in 49 patients. Gastroenterol Clin Biol 1986;10:8-9.
45. Ramond MJ, Valla D, Mosnier JF, et al. Successful endoscopic obturation of gastric varices with butyl cyanoacrylate. Hepatology 1989; 10:488-93.
46. Gotlib JP. Endoscopic obturation of esophageal and gastric varices with a cyanoacrylic tissue adhesive. Can J Gastroenterol 1990;9: 637-8.
47. See A, Florent C, Lamy P, et al. Cerebral infarction following endoscopic obliteration of esophageal varices using isobutyl-2-cyanoacrylate: Report of two cases. Gastroenterol Clin Biol 1986;10:8-9.
48. Soehendra N, Grimm H, Nam V, et al. N-butyl-2-cyanoacrylate: A supplement to endoscopic sclerotherapy. Endoscopy 1987;19:221-4.
49. Reiter A. Induction of sarcomas by the tissue-binding substance Histoacryl-blau in the rat. Z Exp Chir Transplant Kunstliche Organe 1987;20:55-60.
50. Samson D, Marshall D. The use of isobutyl-2-cyanoacrylate in embo lization. Surg Neurol 1987;28:4 (editorial).
51. Koskow PL. Upper lid blepharoplasty: Skin closure achieved with butyl-2-cyanoacrylate. Opthal Surg 1981;12:424-5.
52. Ronis ML, Harwick JD, Fung R, et al. Review of cyanoacrylate tissue glues with emphasis on their otorhinolaryngological applications. Laryngoscope 1984;94:210-3.
53. Matsumoto T. Vienna International Symposium: Tissue adhesives in surgery. Arch Surg 1986;96:226-30.
54. Soehendra N, Grimm H, Nam V, et al. N-butyl-2-cyanoacrylate: A supplement to endoscopic sclerotherapy. Endoscopy 1987;19:221-4.
55. Richter GM, Noeldge G, Palmaz JC, et al. Transjugular intrahepatic portacaval stent shunt: Preliminary clinical results. Radiology 1990; 174:1027-30.
56. Zemel G, Katzen BT, Becker GJ, et al. Percutaneous transjugular portosystemic shunt. J Am Med Assoc 1991;266:390-3.
57. Ring EJ, Lake JR, Roberts JP, et al. Using transjugular intrahepatic portosystemic shunts to control variceal bleeding before liver transplantation. Ann Intern Med 1992;116:304-9.
58. Simpson KJ, Chalmers N, Redhead DN, et al. Transjugular intrahepatic portasystemic stmt shunting for control of acute and recurrent upper gastrointestinal haemorrhage related to portal hypertension. Gut 1993;34:968-73.
59. LaBerge JM, Ring EJ, Gordon RL, et al. Creation of transjugular intrahepatic portosystemic shunts with the wallstent endoprosthesis: Results in 100 patients. Radiology 1993;187:413-20.
60. Rossle M, Haag K, Ochs A, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. N Engl J Med 1994;330:165-71.
61. Haskal ZJ, Cope C. Combined transhepatic and transvenous approach to hepatic vein stenosis after transjugular intrahepatic portosystemic shunt (TIPS). Cardiovasc Intervent Radiol 1994;17:173-5.
62. Nazarian GK, Ferral H, Castaneda ZW, et al. Development of stenoses in transjugular intrahepatic portosystemic shunts. Radiology 1994;192: 231-4.
63. Benner K, Sahagun G, Meyer RA, et al. Shunt patency after transjugular intrahepatic portosystemic shunt (TIPS). Gastroenterology 1993; 104:A876.
64. Haskal ZJ, Pentecost MJ, Soulen MC, et al. Transjugular intrahepatic portosystemic shunt stenosis and revision: Early and midterm results. AIR 1994;163:439-44.
65. Sellinger M, Ochs S, Haag K, et al. Incidence of hepatic encephalopathy and follow-up of liver function in patients with transjugular intrahepatic portosystemic stem-shunt (TIPS). Gastroenterology 1992; 102:A883.
66. Sanyal AJ, Freedman AM, Schiffman ML, et al. Portosystemic encephalopathy (PSE) following transjugular intrahepatic portosystemic shunt (TIPS): A controlled study. Am J Gastroenterol 1992;16:A85.
67. Blei AT. Hepatic encephalopathy in the age of TIPS. Hepatology 1994;20:249-52.
68. Corm HO. Tranjugular intrahepatic portal-system shunts: The state of the art. Hepatology 1993;17:148-58.
69. Sanyal AJ, Freedman AM, Shiffman ML. Transjugular intrahepatic portosystemic shunt for ascites: A preliminary report. Am J Gastroenterol 1992;87:A1305.
70. Ochs A, Sellinger M, Haag K. Transjugular intraheaptic portosystemic stmt-shunt (TIPS) for the treatment of refractory ascites and hepatorenal syndrome: Results of a pilot study. Gastroenterology 1992;102: A862.
71. Helton WS, Belshaw A, Althaus S, et al. Critical appraisal of the angiographic portacaval shunt (TIPS). Am J Surg 1993;165:566-71.
72. Hussey KP. Vasopressin therapy for upper gastrointestinal tract hemorrhage. Has its efficacy been proven? Arch Intern Med 1985;145: 1263-7.
73. Fogel MR, Knauer CM, Andres LL, et al. Continuous intravenous vasopressin in active upper gastrointestinal bleeding. Ann Intern Med 1982;96:565-9.
74. Fort E, Sautereau D, Silvain C, et al. A randomized trial of terlipressin plus nitroglycerin vs. balloon tamponade in the control of acute variceal hemorrhage. Hepatology 1990;11:678-81.
75. Teres J, Planar R, Panes J, et al. Vasopressin/nitroglycerin infusion vs. esophageal tamponade in the treatment of acute variceal bleeding: A randomized controlled trial. Hepatology 1990;11:964-8.
76. Tsai YT, Lay CS, Lai KH, et al. Controlled trial of vasopressin plus nitroglyerin vs vasopresssin alone in the treatment of bleeding esophageal varices. Hepatology 1986;6:406-9.
77. Gimson A, Westaby D, Hegarty J, et al. A randomized trial of vasopressin and vasopressin plus nitroglycerin in the control of acute variceal hemorrhage. Hepatology 1986;6:410-3.
78. Bosch J, Groszmann RJ, Garcia PJ, et al. Association of transdermal nitroglycerin to vasopressin infusion in the treatment of variceal hemorrhage: A placebo-controlled clinical trial. Hepatology 1989;10:962-8.
79. Soderlund C, Magnusson I, Torngren S, et al. Terlipressin (triglycyllysine vasopressin) controls acute bleeding oesophageal varices. A double-blind, randomized, placebo-controlled trial. Scand J Gastroenterol 1990;25:622-30.
80. Freeman JG, Cobden I, Lishman AH, et al. Controlled trial of terlipressin (Glypressin) versus vasopressin in the early treatment of oesophageal varices. Lancet 1982;2:66-8.
81. D'Amico G, Traina M, Vizzini G, et al. Terlipressin or vasopressin plus transdermal nitroglycerin in a treatment strategy for digestive bleeding in cirrhosis. A randomized clinical trial. J Hepatol 1994;20: 206-12.

82. Bosch J, Kravetz D, Rodes J. Effects of somatostatin on hepatic and systemic hemodynamics in patients with cirrhosis of the liver: Comparison with vasopressin. Gastroenterology 1981;80:518-25.
83. Thulin L, Tyden G, Samnegard H, et al. Treatment of bleeding oesophageal varices with somatostatin. Acta Chir Scand 1979;145:395-8.
84. Limberg B, Kommerell B. Somatostatin bleeding esophageal varices: Peer review, anyone? Gastroenterology 1980;78:658-9 (letter).
85. Kravetz D, Bosch J, Teres J, et al. Comparison of intravenous somatostatin and vasopressin infusions in treatment of acute variceal hemorrhage. Hepatology 1984;4:442-6.
86. Walker S, Stiehl A, Raedshc R, et al. Terlipressin in bleeding esophageal varices: A placebo-controlled, double-blind study. Hepatology 1986;6:112-5.
87. Silvain C, Carpentier S, Sautereau 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.
88. Jenkins SA, Baxter JN, Corbett W, et al. A prospective randomised controlled clinical trial comparing somatostatin and vasopressin in controlling acute variceal haemorrhage. Br Med J 1985;290:275-8.
89. Bagarani M, Albertini V, Anza M, et al. Effect of somatostatin in controlling bleeding from esophageal varices. Ital J Surg Sci 1987;17: 21-6.
90. Saari A, Klvilaakso E, Inberg M, et al. Comparison of somatostatin and vasopressin in bleeding esophageal varices. Am J Gastroenterol 1990; 85:804-7.
91. Huang CC, Shhen IS, Chu CM, et al. A prospective randomized controlled trial of sandostatin and vasopressin in the management of acute bleeding esophageal varices. Chang Gung Med J 1992;15:7883.
92. McKee R. Sandostatin therapy of acute oesophageal variceal bleeding. Digestion 1993;1:27-9.
93. Sung J, Chung S, Lai CW, et al. Octreotide infusion or emergency sclerotherapy for variceal haemorrhage. Lancet 1993;342:637-41.
94. Burroughs AK, McCormick PA, Hughes MD, et al. Randomized, double-blind, placebo-controlled trial of somatostatin for variceal bleeding: Emergency control and prevention of early variceal rebleeding. Gastroenterology 1990;99:1388-95.
95. Valenzuela JE, Schubert T, Fogel MR, et al. A multicenter, randomized, double-blind trial of somatostatin in the management of acute hemorrhage from esophageal varices. Hepatology 1989;10:958-61.