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The Use of Vasoconstrictors in Acute Variceal Bleeding: How Long Is Enough?

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Vasoconstrictors are often used as the first line therapy for acute esophageal variceal hemorrhage. They might also be used for a few days after endoscopic therapy to prevent early rebleeding. International guidelines recommend the use of vasoconstrictor therapy when acute esophageal variceal hemorrhage is suspected and continuation of the therapy until 3 to 5 days after endoscopic treatment. However, the duration of use of vasoconstrictors after endoscopic therapy is not clear. This review shows that if variceal bleeding is successfully controlled by endoscopic variceal ligation, the combination of vasoconstrictors can be reduced to less than 1 day.
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Key Words: Acute variceal bleeding; Sclerotherapy; Vasoconstrictors; Banding ligation

INTRODUCTION

Acute esophageal variceal hemorrhage (AEVH) is a major complication of portal hypertension. Previous reports have indicated that AEVH is associated with a mortality rate of 40%, and a high incidence of early rebleeding in the survivors, with an incidence of 30% to 50%.[1] Fortunately, the mortality rate due to AEVH has significantly reduced in the last 2 decades.[2-4] The first introduction of vasoconstrictor therapy in the treatment of variceal hemorrhage was around 1970. Since then, vasoconstrictors have played an important role in the management of AEVH. Subsequently, endoscopic injection sclerotherapy (EIS) became widely popular in the treatment of AEVH. However, EIS alone is still associated with a high incidence of early rebleeding. Thus, a few studies have investigated the efficacy of a combination of endoscopic therapy and vasoconstrictors in the control of acute variceal bleeding.[5-7] Some studies showed that a combination of EIS and vasoconstrictors could achieve a higher hemostatic rate.[8] A meta-analysis of 8 trials in 2003 including 939 patients, demonstrated that the 5-day hemostasis rate was 58% in patients receiving endoscopic therapy alone, while the corresponding figure was 77% in patients receiving a combination therapy, with similar rates of survival and severe adverse events in both groups.[9] Thus, the combination of endoscopic therapy and vasoconstrictors in the management of AEVH has been recommended by nearly all the hepatology and endoscopy guidelines.[2,4,10,11] Continuous use of vasoconstrictors following endoscopic therapy for 3–5 days has become a routine in clinical practice.[11] However, the meta-analysis by Bañares et al. included 3 full-texts and 3 abstracts about EIS therapy, 1 full-text in which both EIS and endoscopic variceal ligation (EVL) were used and 1 full-text paper in which EVL was used as an endoscopic therapy.[9,11] Since EVL has now replaced EIS as the endoscopic therapy of choice to treat AEVH,[4,12] it is necessary to understand the duration for which should the combination of vasoconstrictors be continued following successful EVL.[13,14] Thus, this review tries to analyze the studies conducted with EIS alone versus EIS plus vasoconstrictors and EVL alone versus EVL plus vasoconstrictors respectively, to establish the role of vasoconstrictors as an adjunct to endoscopic therapy in AEVH.

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COMBINATION OF SCLEROTHERAPY AND VASOCONSTRICTORS

Only 6 full-text articles comparing EIS alone and EIS with vasoconstrictors in the management of AEVH have been found so far (Table 1).[5,6,15-18] Possibly owing to the introduction of EVL, studies using a combination of EIS and vasoconstrictors have not been reported after 2005. Although terlipressin is the only vasoactive drug known to increase survival in patients with AEVH, none of the 6 trials used terlipressin as an adjunct therapy. Among the 6 studies, 4 used octreotide, 1 study used somatostatin[15] and 1 study used vapreotide, an analogue of somatostatin.[17] The duration of vasoconstrictor therapy ranged from as short as 48 hours[18] to as long as 29 days.[6] The study by Calés et al. included approximately 30% of the patients who underwent EVL as an endoscopic therapy.[17] The study by Primignani et al. did not indicate the rate of acute hemostasis but showed early rebleeding at 15 days.[6] As shown in Table 1, the rate of hemostasis achieved by EIS alone was between 46% and 78.1%, while that achieved with combination therapy ranged between 66% and 88%. All the 6 trials except the study by Primignani et al., proved the superiority of combining EIS and vasoconstrictors over EIS alone, in the control of AEVH.[6] However, the rate of hemostasis with EIS alone in all these trials was quite lower than that in other studies.[19] This could explain the superiority of combining endoscopic therapy with vasoconstrictors. On the other hand, a combination of EIS with vasoconstrictors did not improve the survival over EIS alone.

COMBINATION OF BANDING LIGATION AND VASOCONSTRICTORS

Since EVL has replaced sclerotherapy as the endoscopic therapy of choice for AEVH,[12] a combination therapy with EVL and vasoconstrictors has become popular in recent years. Sung et al. was the first to prove that a combination of EVL and octreotide was superior to EVL alone in the management of AEVH.[7] However, the hemostasis rate achieved by EVL was only 56%, significantly lower than that seen in most other studies.[4,12,13] Thus, the combination of EVL with

Table 1. Comparison of Acute Hemostasis between Sclerotherapy Alone versus Sclerotherapy Plus Vasoconstrictors

Study	Sclerotherapy alone	Sclerotherapy+Octreotide	Sclerotherapy+Somatostatin
Besson et al. (1995)[5] (*n*=199)	71%	87%	
Primignani et al. (1995)[6] (*n*=58)[a)]	78.1%	80.8%	
Avgerinos et al. (1997)[15] (*n*=205)	46%		66%
Zuberi et al. (2000)[16] (*n*=70)	62.8%	88.6%	
Calès et al. (2001)[17] (*n*=196)[b)]	50%		66%
Shah et al. (2005)[18] (*n*=105)	61.1%	86.2%	

[a)]The hemostatic rate shown was at day 15.
[b)]Enrolled subjects about 50% received sclerotherapy, 30% received ligation; Patients received vapreotide instead of somatostatin.

Table 2. Variceal Bleeding Controlled with Banding Ligation Alone or Combined with Pharmacological Therapy

Study	Ligation alone	Ligation +Octreotide	Ligation +Somatostatin	Ligation +Terlipressin
Sung et al. (1995)[7] (*n*=100)	56%	87%		
Lo et al. (1997)[13] (*n*=37)	97%			
Villanueva et al. (2006)[20] (*n*=90)			90%	
Abid et al. (2009)[21] (*n*=324)		95.6%		92.6%
Azam et al. (2012)[22] (*n*=130)				98.5%[a)] / 100%[b)]
Lo et al. (2013)[24] (*n*=118)	98%			96%
Seo et al. (2014)[23] (*n*=780)		83.8%	83.4%	86.2%
Salim et al. (2017)[25] (*n*=67)	95.1%	-	-	-

[a)]Ligation+Terlipressin infusion for 72 hours.
[b)]Ligation+Terlipressin infusion for 24 hours.

vasoconstrictors can potentially enhance the efficacy in hemostasis. Since controlled studies comparing EVL alone and the combination of vasoconstrictors with EVL are quite few, Table 2 shows some related figures of similar studies. Our study comparing EVL and EIS alone in the control of active bleeding varices showed that EVL alone could arrest 97% of the bleeding episodes.[13] Similarly, Villanueva et al. showed that the use of somatostatin with EVL instead of sclerotherapy in the treatment of AEVH significantly improved the hemostasis rate up to 90%.[20] Regarding the choice of vasoconstrictors, one study showed that terlipressin was not inferior to octreotide as an adjuvant therapy with EVL for the control of AEVH, i.e., 92.6% vs. 95.6%.[21] Moreover, a study from Egypt showed that a short course of adjuvant terlipressin (i.e., 24 hours) was as effective as a 72 hour therapy with successful EVL in achieving a rate of acute hemostasis of 100% and 98.5%, respectively.[22] Another study from Korea also showed no difference between terlipressin, somatostatin and octreotide as an adjuvant to EVL with the 5-day hemostasis rate of AEVH being 86.2%, 83.4% and 83.8%, respectively.[23] Since ligation ulcers are frequently encountered in patients receiving EVL, we performed a study to evaluate proton pump inhibitor versus terlipressin as an adjunctive therapy to patients with successful EVL.[24] Our trial showed that EVL with proton pump inhibitor (without vasoconstrictors) could achieve a 98% hemostasis rate, similar to 96% achieved by EVL plus terlipressin. In a single arm study, Salim et al. demonstrated that EVL alone could achieve an acute hemostasis rate of 95.1%.[25] Based on these studies, it is clear that EVL alone can achieve an acute hemostasis rate ranging between 56% and 98%. The corresponding rates with a combination of EVL and vasoconstrictors were between 83.4% and 100%. In fact, only the first study by Sung et al. in 1995 showed that EVL alone achieved an acute hemostasis rate as low as 56%.[7] Most other studies revealed that EVL alone could achieve acute hemostasis up to 90%.[12,13,24,25]

OPTIMAL DURATION OF VASOCONSTRICTOR THERAPY

For a long time, vasoconstrictors have been considered as the best adjuvant to endoscopic therapy, to arrest AEVH. The rationale of combining vasoconstrictors with endoscopic therapy is to reduce the portal pressure and variceal blood flow as a preventive for very early rebleeding. Both the meta-analyses published between 1999 and 2003 showed that a combination of vasoconstrictors and endoscopic therapy was superior to endoscopic therapy alone in the control of AEVH.[8,9] However, both meta-analyses included trials that mostly used EIS as an endoscopic therapy. Since EIS is associated with a high incidence of rebleeding, EIS should be combined with vasoconstrictors to achieve a higher rate of hemostasis. Even with a combination of vasoconstrictors, the successful 5-day hemostasis with EIS was only in the range of 66% and 88%. By contrast, EVL alone appears to be as effective as the combination of vasoconstrictors and EVL in the control of AEVH. Additionally, no difference was found between the combination of vasoconstrictors such as octreotide, somatostatin or terlipressin with EVL. It can thus be construed that all 3 vasoconstrictors are equally efficient as an adjunct therapy to EVL.[26]

It is now recommended that vasoconstrictors should be administered when an episode of AEVH is suspected. It is also believed that vasoconstrictors should be continued for 2–5 days after endoscopic therapy.[2,4,10,11] For example, 2 mg of terlipressin every 4 hours in the initial 48 hours until control of bleeding is recommended, followed by 1 mg every 4 hours for another 3 days to prevent rebleeding.[11] Though vasoconstrictors other than vasopressin are generally considered quite safe, terlipressin is associated with multiple and moderately severe adverse events.[24] Combination with vasoconstrictors up to 5 days after successful EVL increases medical the expenditure and adverse events, with the likelihood of an increase in the hospitalization days. It has been found that the rebleeding is most likely to occur in the first 5 days after AEVH;[27] thus, a longer duration of treatment with vasoactive drugs is considered as a practical approach. However, most studies revealed that EVL alone could achieve acute hemostasis in more than 95% of the cases,[12,13] with a rebleeding rate of 5% in one month.[13] Consequently, the combination with vasoconstrictors up to 5 days after EVL might be indicated only in endoscopic therapy failure cases. Once EVL has achieved a successful hemostasis on endoscopy, the combination of vasoconstrictors for only 24 hours[22] or discontinuation of vasoconstrictors soon after endoscopic therapy, does not seem to increase the risk of rebleeding.[13,24,25] It is necessary to conduct a head to head comparison study between EVL alone and EVL combination therapy with vasoconstrictors in the therapy of AEVH. However, EVL alone to treat AEVH would be considered unethical, since all related guidelines recommend that EVL should be combined with vasoconstrictors to treat AEVH.[10,11] If vasoconstrictors can be discontinued early in the management of AEVH, beta blockers can be instituted earlier to prevent variceal bleeding.[28] On the other hand, for patients belonging to Child-Pugh class C or hepatic venous pressure gradient ≥20 mm Hg, a high risk of rebleeding is observed.[29] Combination with vasoconstrictors for up to 5 days and early transjugular intrahepatic portosystemic stent shunt in this setting might be indicated.[30]

CONCLUSIONS

Vasoconstrictors should be administered when AEVH is suspected. It is mandatory to continue vasoconstrictor therapy for up to 5 days if an EIS is performed to arrest the AEVH. If EVL is performed to treat the bleeding varices, the combination therapy with vasoconstrictors can be shortened to 24 hours or discontinued soon after successful ligation of the bleeding varices on endoscopy. Combination therapy with vasoconstrictors up to 5 days could be used for patients who fail to respond to EVL therapy. These would be approximately 5%–15% of patients undergoing EVL to treat AEVH.

Conflicts of Interest

The author has no financial conflicts of interest.

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