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ORIGINAL ARTICLE

Worldwide practices for pharmacologic therapy in esophageal variceal hemorrhage

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Abstract

Objective. Pharmacologic therapy (PT) for patients with esophageal variceal hemorrhage (EVH) may improve outcomes. The aim of this article is to assess the current and potential future use of PT in cirrhotic patients with EVH. ***Material and methods.*** We validated a 13-question survey about PT and physician preferences for specific therapies in cirrhotics with EVH; 2349 randomly selected Gastroenterology and Hepatology physicians worldwide were surveyed. The survey addressed institutional location, octreotide or terlipressin use and preference, PT prior to endoscopy, and future plans for terlipressin use, if not already instituted. ***Results.*** Of those surveyed, 337 (14%) email addresses were nonfunctioning. Of the remaining 2012 surveyed, 371 (18%) responses were collected. Nearly two-thirds of physicians preferred to use PT prior to endoscopic intervention ($p < 0.001$). Nearly 70% of respondents only had octreotide available, while 6% had only terlipressin. Of the 24% having both octreotide and terlipressin available, 55% preferred terlipressin compared to 38% who preferred octreotide ($p < 0.001$). Of those physicians currently not using terlipressin because of its unavailability, 93% would be willing to use it if it were readily available. ***Conclusions.*** Of physicians with both terlipressin and octreotide available for treatment of EVH in cirrhotics, most prefer terlipressin, even if currently unavailable.

Key Words: *cirrhosis, octreotide, portal hypertension, terlipressin*

Introduction

It is estimated that 5.5 million people in the USA have cirrhosis, which currently is the second leading cause of digestive disease related mortality [1]. Although the exact prevalence worldwide is unknown, many individuals have undiagnosed non-alcoholic steatohepatitis (NASH), hepatitis C and compensated cirrhosis, thereby underestimating its prevalence [2]. One of the complications of cirrhosis is the development of gastroesophageal varices, which ranges anywhere from 43% to 72% of those diagnosed with cirrhosis, and is dependent on the Child–Turcotte–Pugh (CTP) class [3]. Development and growth of gastroesophageal varices have been estimated to occur at a rate of 7% per year and seen in up to 35% by year 3 [4,5], with the first variceal hemorrhage occurring at a rate of 5–15% during the first year depending on variceal size [6]. Although mortality from esophageal variceal hemorrhage (EVH) ranges from 0% to 30% depending on CTP class, the 1-year variceal hemorrhage recurrence rate is about 60% [7–9].

Over the past few decades, pharmacologic therapies for acute EVH have become an attractive first-line approach because they are safe, appear to be effective, and can be easily administered [10]. While many different compounds have been studied, octreotide is used most commonly in the USA. Octreotide is a synthetic octapeptide of somatostatin, sharing within the latter, four amino acids that are responsible for its biological activity [11]. Its mechanism of action is believed to be by reducing splanchnic blood flow and

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decreasing portal pressures, and thus, reducing collateral and azygos blood flow [12,13]. It has also been shown to spare systemic circulatory effects making it safe to use without special monitoring [10].

Although octreotide is available worldwide, terlipressin has been used extensively for treatment of acute EVH in countries other than the USA [14]. Terlipressin (triglycyl lysine vasopressin) is an analogue of vasopressin with longer biological activity and fewer cardiac, bowel and peripheral ischemic side effects since terlipressin unlike vasopressin, (most likely related to the fact that it) lacks plasminogen activating activity [15,16]. It can be administered as a bolus intravenous (IV) injection as well as by IV infusion and is the only vasoactive agent that has shown to improve survival [6,17].

Despite data indicating that terlipressin is safe and appears to be as effective as octreotide in EVH, it remains unavailable in the USA [15]. We hypothesized that if both octreotide and terlipressin were both available, most physicians would be willing to use terlipressin, and moreover, based on the available data, may even prefer its use over octreotide in cirrhotic patients with EVH. Therefore, our aim was to measure the use and preferences concerning octreotide and terlipressin using a worldwide survey instrument.

Methods

We validated a 13-question survey about pharmacologic therapy (PT) and physician preferences for specific therapies in cirrhotics with EVH. The survey inquired about number of EVH patients treated per month, number of physicians in the practice, location and practice type (academic vs. private institution), octreotide or terlipressin availability, use and preference, year terlipressin was implemented in practice, use of PT to direct patient care prior to endoscopy, and future plans specifically focused on terlipressin use, if not already instituted (Table I).

Two thousand three hundred and forty-nine gastroenterologists and hepatologists were randomly selected from a computer database using the 2009 American Association for the Study of Liver Diseases (AASLD), American Gastroenterological Association (AGA), or American Society for Gastrointestinal Endoscopy (ASGE) member directories from a total of more than 30,000 worldwide members. Surveys were sent to physicians from North and South America, Africa, Asia, Australia, and Europe. Physicians from all locations, practice type, and academic ranks were included.

Internal validation of the questionnaire was performed by distributing the survey to over 30 gastroenterology and hepatology faculty and fellows at our institution. We asked each individual about the questions and their content, clarity and ease of understanding of each question posed. After each question, we designated an area for each physician to either circle "yes" or "no" if the question was appropriate and understandable for the target audience. Those that circled "no" further characterized the specific area of confusion within each question and suggested ways in which each question could be improved so as to be better understood. After validation was complete, we used SurveyMonkey® to create the online survey. A total of three reminder emails were sent during the study period to increase the response rate. Each email contained a cover letter explaining the purpose and content of the survey, a survey link to access the survey, the confidentiality of the survey, and an optional link to remove oneself from the email list.

Data collection and statistical analyses were performed using Microsoft Office Excel 2007, version 12 (Microsoft Inc., Redmond, WA, USA). A chi-squared test was used to analyze differences in proportions between various groups. A p-value of < 0.05 was considered significant.

Results

Of the 2349 randomly selected gastroenterology and hepatology physicians contacted worldwide from 25 January 2011 to 25 April 2011, 337 (14%) email addresses were undeliverable. Of the 2012 contactable physicians, we received 371 (18.4%) responses, which were determined *a priori* to be sufficient based on a previous survey of similar size and target audience [18]. Nearly 15% of responses were from women (Table II), while over half of respondents completed fellowship within the past 20 years. Hospital affiliations included 243/371 (66%) from academic/university, 109/371 (29%) from private practice/community, and 19/371 (5%) from Veterans Affairs (VA) institutions. Responses were received primarily from physicians in North America, Europe, Asia, and Australia. Most respondents worked in large groups, with 70% of physicians working in groups of greater than 6 physicians and nearly one-third working in groups of greater than 15 physicians. The cohort appeared to be highly active at EVH treatment, with slightly more than two-thirds treating more than five episodes of EVH per month. About one-third of respondents started using terlipressin prior to the year 2000, while nearly another third were unaware of when terlipressin use was implemented.

In addition to asking about current pharmacologic therapies and preferences of physicians in EVH, we

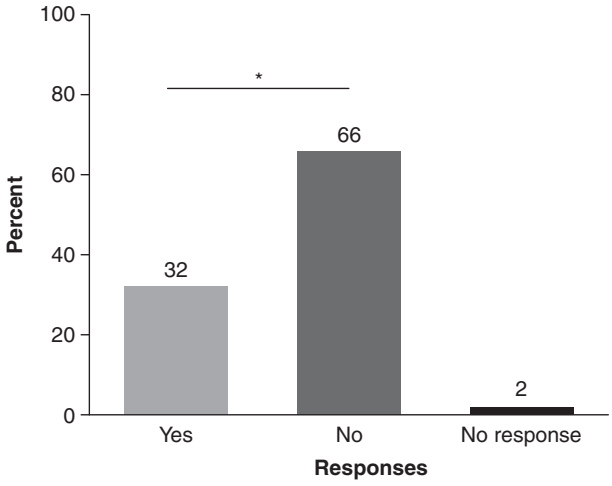

Figure 1. Endoscopic intervention in upper GI bleed prior to pharmacologic therapy. Responses to the survey question about whether providers perform endoscopy in cirrhotic patients with upper GI bleed prior to instituting pharmacological therapy (32% would perform endoscopy prior to pharmacologic therapy vs. 66% who preferred pharmacologic therapy prior to endoscopy in suspected EVH, $*p < 0.001$).

inquired about endoscopic practices prior to initiating pharmacologic therapies. Interestingly, we found that nearly one-third (118/371) of physicians perform endoscopic interventions in cirrhotic patients with acute upper gastrointestinal bleeding prior to initiating PT (Figure 1), which is in contrast to what is suggested in the AASLD guidelines for EVH.

Of the 371 respondents, in nearly 70%, only octreotide was available. Consistent with the large proportion of US respondents (Table II), 6% had terlipressin only, while 24% had both octreotide and terlipressin. Interestingly, 1% had somatostatin only (Figure 2). Among those physicians who responded as having both octreotide and terlipressin available ($n = 87$), the majority preferred terlipressin, compared to octreotide, while 7% had no preference (Figure 3; $p < 0.001$). Physicians currently not using terlipressin because of its unavailability ($n = 262$), an overwhelming majority (93%) would be willing to use it if it were readily available (Figure 4; $p < 0.001$ for comparison of those preferring terlipressin to those who did not prefer terlipressin). Reluctance in using terlipressin appeared to be a result of unfamiliarity with the product. Additionally, limited data and concern about cost were also noted to be important. However, a belief that other therapies were more effective than terlipressin was uncommon (Table III). Physicians working in a university-based practice (including VA medical centers), were more likely to use terlipressin 87% compared to those in community hospitals 13% ($p < 0.001$).

Table I. Survey instrument.

1. Roughly how many patients with esophageal variceal hemorrhage are treated at your facility per month?
   - Less than 5
   - 5–10
   - 11–20
   - Greater than 20

2. Is your institution affiliated with?
   - Academics/University Hospital(s)
   - Private Practice/Community Hospital
   - Veterans Affairs

3. Which pharmacologic agent is available at your institution?
   - Octreotide
   - Terlipressin
   - Octreotide and terlipressin

4. Which pharmacologic agent do you prefer?
   - Octreotide
   - Terlipressin
   - No preference

5. What pharmacologic agent(s) do you primarily use to treat cirrhotic patients with acute upper GI bleed?
   - IV octreotide
   - IV terlipressin
   - IV octreotide or terlipressin
   - Both IV octreotide and IV PPI
   - Both IV terlipressin and IV PPI
   - Other (please specify)

6. If your institution currently uses terlipressin for esophageal variceal bleeding, when did this begin?
   - Pre-2000
   - 2001
   - 2002
   - 2003
   - 2004
   - 2005
   - 2006
   - 2007
   - 2008
   - 2009
   - 2010
   - 2011
   - Not applicable

7. If terlipressin is NOT currently used at your institution for esophageal variceal bleeding, would you be willing to use it if it were available at your institution?
   - Yes
   - No
   - Terlipressin is already being used at our institution

8. If you would NOT use terlipressin if it were available, what would be the main reason for NOT considering its use?
   - Not familiar with the product
   - Limited data
   - Cost
   - Other (please specify)

9. Do you usually perform endoscopic intervention in acute upper GI bleed (in cirrhotics) prior to pharmacological therapy?
   - Yes
   - No

10. Where does your practice reside?
   - Africa
   - Asia
   - Australia

Canada
Europe
Middle East
South America
USA

11. How many Gastroenterologists and/or Hepatologists are in your practice?
1–2
3–5
6–10
11–15
16+

12. Your gender is?
Male
Female

13. What year did you graduate from Gastroenterology and/or Hepatology fellowship?
1931–1940
1941–1950
1951–1960
1961–1970
1971–1980
1981–1990
1991–2000
2001–2010
Currently in fellowship

IV, Intravenous; PPI, Proton pump inhibitors; GI, Gastrointestinal.

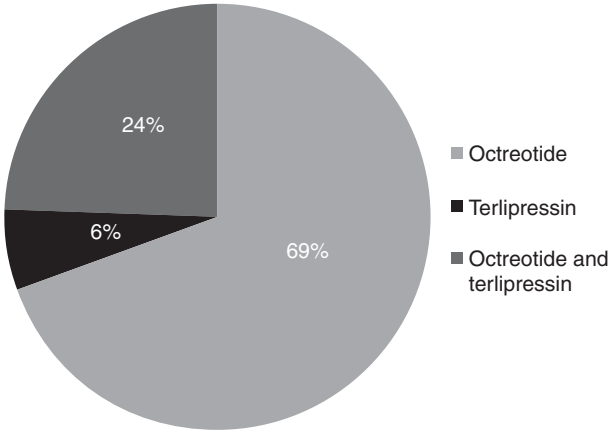

Figure 2. Pharmacologic agent availability. A pie chart showing the availability of pharmacologic agents at their own institution is shown. Not shown in the pie chart is the 1% having somatostatin only.

Discussion

With this survey, we learned several important details concerning the use of pharmacologic agents for EVH. First, while vasoactive drugs including octreotide and terlipressin have been the mainstay of PT in cirrhotic patients with EVH, we found that only two-thirds of respondents worldwide use these agents prior to endoscopic therapy, which is not consistent with current

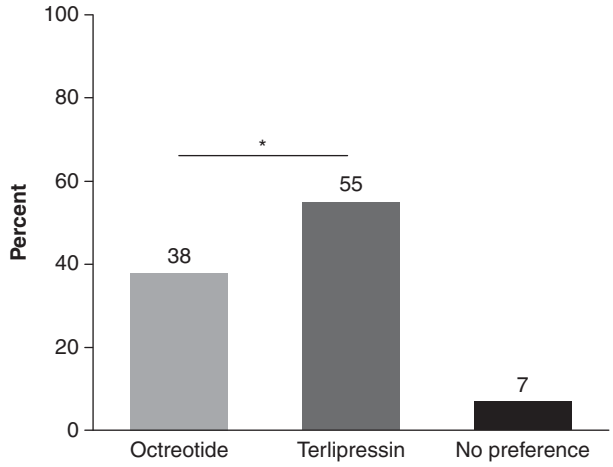

Figure 3. Preferences when both octreotide and terlipressin are available. The graph depicts the preferences of the 87 survey respondents that had both octreotide and terlipressin available (38% of practitioners preferred using octreotide compared to 55% who preferred using terlipressin in EVH, $*p < 0.001$).

AASLD guidelines [15]. We also found that given the choice of either octreotide or terlipressin, the majority would prefer the use of terlipressin [6].

We were surprised that not all practitioners routinely give PT prior to endoscopy in patients with suspected EVH. We considered the possibility that the question included in the survey was confusing and that the responses may not have reflected real-life practice. However, during validation of the questionnaire, we verified that practitioners clearly understood the question. Another possible explanation for this result might be that local practice patterns dictate care. For example, one center may have a lower EVH rate in cirrhotic patients than other institutions. Stated in another way, if a practitioner realized that EVH accounts for up to 60% of upper GI hemorrhage in their cirrhotic population [19], they would likely begin PT prior to endoscopy. On the other hand, if their concern for EVH is low, they may elect to perform endoscopy prior to implementation of PT. However, the finding that one-third of providers intentionally perform endoscopy prior to giving pharmacological therapy in patients with cirrhosis and possible EVH is not in line with current AASLD guidelines, in which routine administration of PT is recommended immediately, and prior to endoscopic therapy [15]. Of particular note, a meta-analysis suggested that PT should be considered first-line treatment of variceal bleeding [20], followed by endoscopic therapy within 12 h if EVH is suspected [15,21]. A meta-analysis reported that pharmacological followed by endoscopic therapy improved hemostasis initially, and by day 5, without increasing severe adverse events [22]. Since terlipressin is

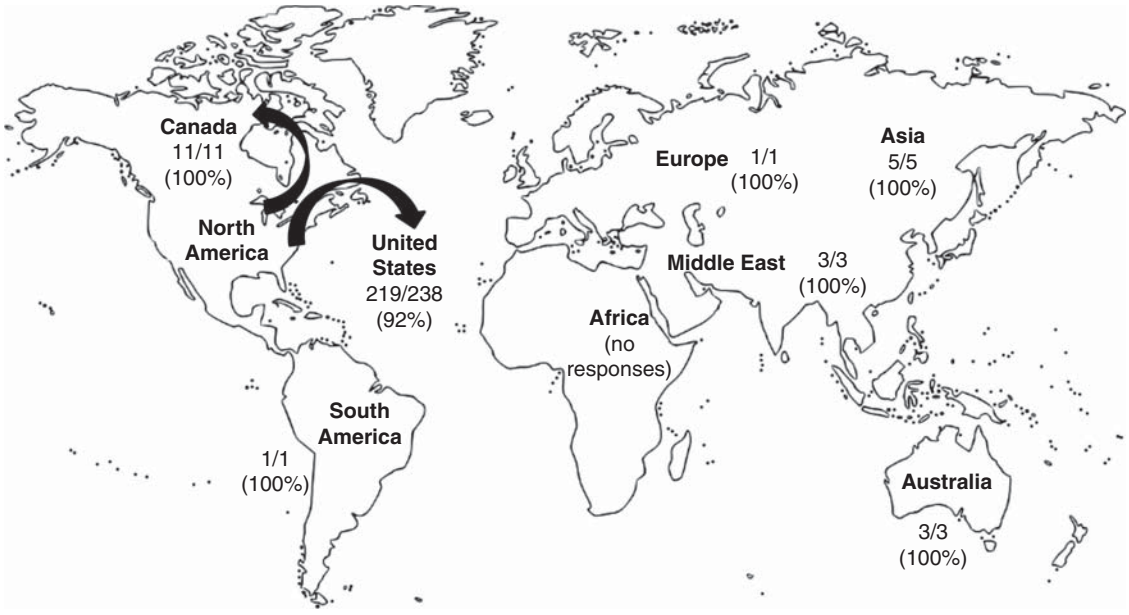

Figure 4. Willingness to use terlipressin based on location. Shown in the world map is the proportion of the 262 practitioners in different areas of the world not using terlipressin due to its unavailability, who would be willing to use it if it became available. There were no responses from Africa. Nineteen practioners (all in the USA) would not be willing to use terlipressin if it were made available (thus, in this subgroup, 93% of practitioners worldwide would use terlipressin vs. 7% who would not, $p < 0.001$).

considered safe and effective in controlling acute EVH while decreasing mortality, it has been routinely implemented as the first line of PT where available [17,23,24]. Although meta-analyses of octreotide have demonstrated equivocal benefit [25,26], and trials of somatostatin analogues reveal negligible benefit [27], octreotide is still used commonly in the USA for EVH. The choice concerning whether to use octreotide or terlipressin when both are available could be related to the CTP class at the time of presentation of EVH. Patients presenting with EVH who are CTP-A, might be satisfactorily treated with octreotide since these patients have a better overall prognosis, while CTP-C patients might benefit from a more effective agent such as terlipressin since they have poorer liver function and a greater risk of a poor outcome. Of note, tachyphylaxis appears to occur with octreotide resulting in only transient reduction in portal pressures, while terlipressin appears to be associated with more sustained hemodynamic effects [28,29].

Our survey also found that academic practices were nearly seven times more likely to use terlipressin than community hospitals. Our data also suggests that the majority of respondents who do not currently have access to terlipressin would consider its use if it were available. Further, of those that had both octreotide and terlipressin available, the majority preferred terlipressin. Finally, in those reluctant to use terlipressin ($n = 19$), most reported unfamiliarity of the product, as currently terlipressin in not approved by the food and drug administration in the USA for EVH [15]. These data suggest that most providers believe that terlipressin is effective, and that for some practitioners, education may be helpful.

We recognize potential limitations of our study. First, the response rate was 18%; while this may be considered low, this is highly consistent with the response rate of other similar published surveys [18]. Thus, the response rate for this study should be considered good. In addition, although it is known that terlipressin is not available in the USA, a higher than expected number of US practitioners, compared to those from other parts of the world (where terlipressin is readily available) responded (Table II). The response rate and enthusiasm from the US practitioners in using terlipressin if made available may be the first step in considering future prospective trials of this orphan drug in the USA. Additionally, the majority of responses were from individuals working in academic institutions. While it is possible that their practices are different from those in community practice, we suspect that this is unlikely since academic physicians train and educate those in community practices, informing their practice patterns. Finally, the survey was a self initiated survey and respondents may have been more attuned to the topic of portal hypertension and EVH than non-responders. This could have led to bias.

Table II. Features of the study group.

Gender	*n* = 371 (%)
Female	54 (14.6)
Male	301 (81.1)
Not stated	16 (4.3)
Practice affiliation	Response (%)
University/VA	262 (70.6)
Community hospitals	109 (29.4)
Practice location	Response (%)
USA	248 (66.8)
Europe	53 (14.3)
Asia	17 (4.6)
Australia	12 (3.2)
Canada	11 (3.0)
South America	8 (2.2)
Middle East	8 (2.2)
Africa	2 (0.5)
Not stated	12 (3.2)
Physicians in each practice	Response (%)
1–2	30 (8.1)
3–5	72 (19.4)
6–10	92 (24.8)
11–15	64 (17.3)
> 16	103 (27.8)
No response	10 (2.7)
Treatment of EVH patients per month	Response (%)
< 5	112 (30.2)
5–10	137 (36.9)
11–20	65 (17.5)
> 20	55 (14.8)
Not stated	2 (0.5)
Year terlipressin instituted if available	Response (%)
Prior to 2000	35 (32)
2001–2005	22 (20)
2006–2010	13 (12)
After 2011	0 (0)
Unsure or unknown	39 (36)
Year graduated from fellowship	Response (%)
1941–1950	1 (0.3)
1951–1960	2 (0.5)
1961–1970	7 (1.9)
1971–1980	46 (12.4)
1981–1990	70 (18.9)
1991–2000	85 (22.9)
2001–2010	121 (32.6)
Currently in fellowship	26 (7)
Not stated	13 (3.5)

VA:Veterans Affairs; EVH: Esophageal variceal hemorrhage.

Table III. Reasons that providers would not use terlipressin.

Reasons for reluctance in using terlipressin	*n* = 19 (%)
Unfamiliar with the product	11 (57.9)
Limited data	5 (26.3)
Concerned about cost	2 (10.5)
Believed beta-blockers and octreotide are more effective	1 (5.3)

As the worldwide prevalence of cirrhosis rises, and the number of patients with cirrhosis is projected to increase greatly in the next several decades [30], it will become more and more important for practitioners to become experts in the management of complications of cirrhosis, including EVH. Hence, timely, safe, and effective use of vasoactive agents will become an important element in management of this ever-enlarging group of patients.

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