Endoscopic Sclerotherapy of Esophageal Varices

Edited by

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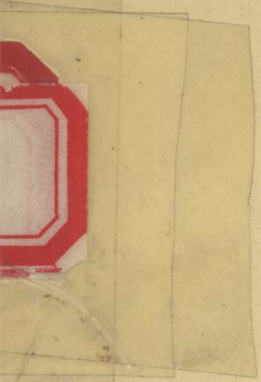

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Contents

Preface

Endoscopic sclerotherapy of esophageal varices is not new, its inception being over 40 years ago. However, the recent widespread and increasing interest in this procedure is remarkable. There are many aspects of sclerotherapy which are as yet unresolved or empiric, not the least of these being questions pertaining to optimum technique. There is much in the way of opinion, but very little data. For patients undergoing sclerotherapy the outcome in terms of beneficial or detrimental effects is now under investigation.

The Tenth Anniversary Gastrointestinal Endoscopy Continuing Education Course of the Cleveland Clinic Education Foundation and the Section of Gastrointestinal Endoscopy of the Department of Gastroenterology of the Cleveland Clinic was offered with these circumstances in mind. This book is based on the syllabus from this course with some modifications. It was fortunate that a distinguished international faculty could be assembled that included many of the recognized leaders in the field of sclerotherapy. Much of their work and thought on this subject is collected in this book. I thank them for their willingness to share their experiences and expertise, and for their efforts on behalf of the course and this publication.

The initial half of this book is devoted to several introductory subjects, which are followed by a number of chapters dealing with special topics. In the second half, eight of the contributors present their personal viewpoints with regard to indications, technique, results, and complications of sclerotherapy. This section was designed for comparison of the various differing approaches to the procedure.

Perhaps the present enthusiasm for endoscopic sclerotherapy will be wholly, or at least partially, justified over the next several years. It is likely that some aspects of the procedure or its application will be modified. Given the seriousness of the problem for which sclerotherapy is intended, one would anticipate, based on the favorable results presented here, that endoscopic sclerotherapy will continue to gain an effective place in the management of variceal hemorrhage. Thus this book represents a point of departure as much as an effort to summarize our knowledge and understanding of endoscopic sclerotherapy at a specific point in time.

PART I

BACKGROUND TOPICS, INVESTIGATIVE APPROACHES, AND SPECIAL INDICATIONS FOR SCLEROTHERAPY

1

The Natural History of Variceal Bleeding

D. Roy Ferguson, M.D.

The brilliant foreground of new therapeutic modalities in the treatment of esophageal variceal bleeding such as endoscopic sclerotherapy, angiosclerotherapy and beta blocker therapy all but hides the supporting background. It is this background of the natural history of bleeding varices which must be examined carefully in order to fully evaluate the foreground figures.

While we all recognize the course of events in variceal bleeding, it remains difficult to study the natural history of bleeding varices. The purpose of this essay is to explore the most significant of this literature in an attempt to delineate: 1) the effect of both time of entry and length of followup; 2) factors affecting survival; and 3) factors affecting rebleeding.

EFFECT OF TIME

In the analysis of survival following bleeding one can measure immediate survival, long term survival, and composites of this. The analysis of Ratnoff and Patek[8] of long-term survival following an initial bout of hematemesis reveals a curve that is strikingly similar to that of Graham and Smith[5] in 1980 (Figure 1). Indeed, despite more than thirty years of time and a variety of treatment modalities, the 45% six-month survival and 28% one-year survival of Ratnoff is not too different from modern statistics. There are, however, some who find that their survival statistics are much better and this is attributed to an improved modality of therapy such as shunt surgery. To what these differences can be attributed has been a great concern. A variety of factors have been found including differences in populations studied according to degree of illness, differences in hepatic reserve, differences in

drinking habits following therapy, and difference in extent and severity of bleeding or time of entry into study. Smith and Graham[10] have summarized the studies to date that have calculated long-range survival and found variations at the one-year level from the lower 36% in the Child's C as reported by Turcotte to a high of 97% reported by Galambos in patients who quit drinking. Some of the studies lump all the patients into cirrhosis including different types of cirrhosis as well as cirrhotics with alcoholic hepatitis. This may affect the outcome as discussed later. Reynolds et al.[9] reported a twelve-year randomized prospective trial of portacaval shunts and attempted to derive the natural history of the varices from the nonshunted patients. Forty-four of 89 patients were randomized to medical therapy ("natural history"). Sixty of the 89 patients who were randomized had more than one episode of upper GI bleeding and the time between bleeding and entry into the randomization was variable. There were a significant number of people who dropped from medical therapy and were operated. Twenty-nine deaths occurred in the medical therapy between this period of time, 23 of these related to bleeding. Again the shape of the survival curve from this study is similar to that of Graham's with only minor variation in the percentage. Obviously, then, the major differences in various studies cannot be accounted for by the course of the long-range survivors since all seem to follow a rather parallel course. Smith and Graham[10] addressed this problem and analyzed the course of 85 consecutive endoscopically verified bleeders. Their own mortality of 43% at six weeks was not unlike others. They noted, however, that by varying the time of entry into the study, hence changing the zero time for calculating survival, they could have achieved statistically different results (of Figure 2) and indeed by applying this criterion to other studies could demonstrate that the key to the differences in long-range survival was in the number of people who died very early in the study. It was their contention that the only way comparative studies could be done would be by controlling the time of randomization and onset of therapy. Of equal importance, perhaps, is that if the curve is considered to be a biexponetial curve then separate analysis of the early deaths and late deaths can be carried out with regard to factors that might influence survival.

FACTORS THAT AFFECT SURVIVAL

The major, if somewhat trite, observation can be made that the best predictor of long-term survival is survival of the first bleed based on all of the studies that have been done. If a somewhat arbitrary time of six weeks (as was done by Graham) is used as the separation point, one can separately analyze early and late death with regard to factors contributing to this. Again, this time frame appears to be a valid time frame since the majority of the

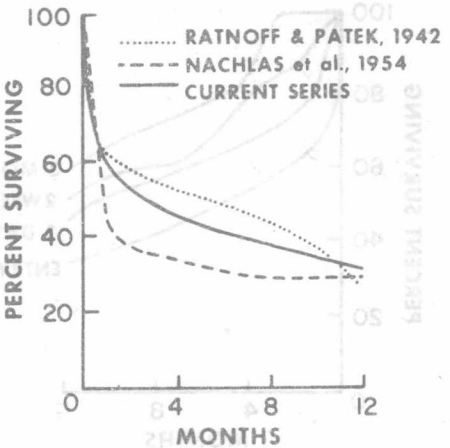

Figure 1. Comparison of survival curves obtained over four decades. From: Graham and Smith: The Course of Patients After Variceal Hemorrhage. Gastroenterology 80:800–9, 1981.

early deaths and the two different curve slopes can be constructed at about one to two months, thereby allowing some comparison among studies. In Graham's study, death occurred in 42% of the medically treated group in this period. Three quarters of this 42% died within the first week. About 60% of the deaths occurred due to bleeding or rebleeding within this period; 26% due to hepatic failure and 14% due to other causes including pneumonia and complications directly related to therapy. This compared to deaths occurring after six weeks where about one-third were due to bleeding, one-third due to hepatic failure and one-third due to other causes including infection, etc. The immediate difficulty of comparing previous studies is demonstrated by the lack of ability to separate the two time periods with regard to the complications.

However, Olsson[7] in a retrospective pathologic study found that of 100 patients who had had bleeding varices, 46% had died within the first month as a result of bleeding or rebleeding. Comparison of the long-range survival can be more readily done, although the lack of separating it from the early deaths in the long-range statistics does alter the figures to some extent. Forty-four percent of the survivors of more than one month in Olsson's pathologic review died in the follow-up period of "bleeding-related deaths". Nachlas et al.[11] described a 28% one-year survival rate and noted that 60% of bleeding cirrhotics would die of a first hemorrhage which unfortunately includes other than variceal bleeding. Of the 44% surviving hemorrhage, two-thirds would be alive longer than one year.

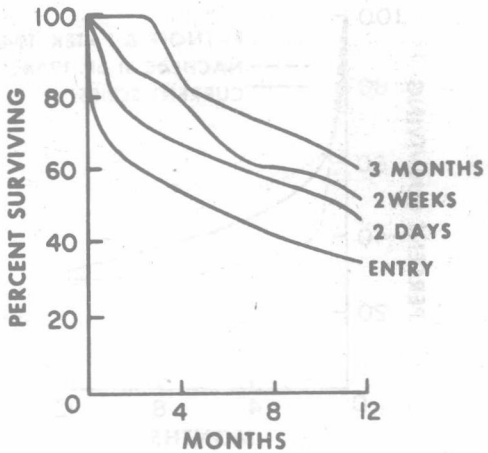

Figure 2. Comparison of the effect of varying "0" time for calculating survival from entry to 2 days, 2 weeks, and 3 months. From: Graham and Smith: The Course of Patients After Variceal Hemorrhage. Gastroenterology 80:800–9, 1981.

Graham attempted to distinguish those who died from bleeding from those who died from other causes but determined that there were no specific discriminating factors. While the overall survival was adversely affected by a number of factors including severity of liver disease as judged by an SGOT greater than 100 units or a Child's classification of C, this did not reflect on those who died of active bleeding. Likewise the presence of ascites was a predictor of decreased survival but not of the type of death. Both in the acute period and in the longer survival period no new factors affecting survival were identified except for the possibility of active bleeding seen at endoscopy in addition to the markers of severe liver disease.

It can be seen, therefore, that in factors affecting survival, studies need to concentrate on carefully reviewing both the long-term and short-term survival for those features which may distinguish those who will die in the first six weeks and those who will survive for a longer period of time. Indeed the survival curves of those who survived beyond the first year are virtually identical with those with cirrhosis without antecedent bleeding. Studies of any therapy in the acute phase will then have to have groups matched with as many factors as can be identified that *may* affect survival.

FACTORS THAT AFFECT REBLEEDING

It is of note that Graham was unable to define features that delineated those who died from bleeding as opposed to those who died from other causes

in parts of his survival curve. He did note, however, that the serum albumin concentration approached significance, with those dying from other causes having a lower serum albumin than those dying from bleeding. Another factor which may have some significance is that of the ten patients with massive ascites on admission, eight died of bleeding. Also it is of some note that while the Child's classification may have predicted the ultimate decreased survival it did not have any correlation with the risk of rebleeding or death from bleeding. To date there has been no good information to suggest which people might rebleed. Indeed the closest clue seems to be the presence or absence of portal hypertension. Lebrec[6] noted that the overall risk of gastrointestinal bleeding from all causes was higher in patients with larger sized esophageal varices than in those with no or small-sized varices. He did not, however, find any correlation with portal hypertension. Conn[2], in an accompanying editorial, noted that with the exception of one patient with small varices and a high portal pressure, the remaining three patients had small varices and a low portal pressure and this statistically significantly changed the difference between those who bled with large varices and those who did not bleed with small varices.

A number of studies have alluded to, or demonstrated that, continued consumption of alcohol appeared to affect the survival of patients adversely. The difficulty in guaranteeing that a patient does not continue to use alcohol has marred many of the studies that have been done to delineate this risk. Dagradi[3], however, in a study designed to evaluate the natural history of esophageal varices noted that in 75 patients with histologically proven cirrhosis who continued to drink, there was a trend for the varices to enlarge in caliber and to extend in longitudinal extent. Twenty-eight (or 37%) of the patients ruptured their varices during the followup period of observation of greater than five years. In fifteen patients selected because they quit using alcohol, observed for a somewhat shorter period of less than four years, there was a gradual diminution of caliber and extent of the varices in 80%. No ruptures of the esophageal varices occurred in this group. A group selected from the group of 85 drinking cirrhotics with varices but who were matched otherwise had a mortality of greater than 50% and a rebleeding rate of about 50%. The linkage between decreased survival and continued alcohol use has been proposed by a number of studies and the Dagradi study cites the correlation between continued alcohol use and varices both as to enlargement and rupture. It is tempting to believe that portal pressure and the presence or absence of ascites as perhaps a marker of portal pressure increase and may have predictive value in the risk of rebleeding.

The quantitation of rebleeding following the first bleed is not available. It would appear from the Graham data that patients who survive the initial bleed, (i.e. "survivors") and who have the same risk of mortality as other cirrhotics can on subsequent bleeds have massive bleeds.

SUMMARY

The studies that are available, particularly the Graham and Smith studies, have indicated that the curve of survival is biexponential with a large group dying in the initial period right after the bleed and that the group of survivors of this initial period, no matter what therapy is done in this initial period, have similar survival characteristics. The time of entry into a study when dated from the time of presentation with the bleed can shift the overall survival curve and it is this early group that must be studied for future alterations in mortality. A number of factors have been demonstrated not to affect the survivability, and the same factors that have been noted in the past, i.e. primarily the severity of the liver disease and the extent of hepatic reserve, correlate with survival. No good factors were identified to predict rebleeding. The continued use of alcohol in alcoholic cirrhosis may correlate with an increasing size of varices and possibly correlate with rebleeding as judged by Dagradi's data.

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2

The Medical Therapy for Variceal Hemorrhage

William D. Carey, M.D.

Cirrhosis is the commonest disease resulting in esophageal varices. As a result, patients who bleed from varices have *two* serious disorders, acute bleeding and its sequellae, and a profound underlying chronic disease. This factor is significant because the severity of the underlying disease will have an important bearing on the success or failure of various medical or surgical therapies.

The treatment of varices usually follows a bleeding episode. Patients with varices which have never bled may be identified during the course of evaluation for liver disease or because upper intestinal endoscopy has been done for other reasons. Attempts to *prevent* the first bleed in such patients by means of decompressive portal shunt operations were tried and abandoned many years ago because it reduced survival rates in nearly all clinical trials[1–4]. Newer pharmacologic measures and/or sclerosis of varices may rekindle interest in *prophylactic* treatment of varices but no recommendations to do this can be made at present. The discussion which follows will consider the management of the patient who has bled at least once from esophageal or gastric varices.

It is best to consider separately the management of acute variceal bleeding, on the one hand, and the more long-term problem of preventing recurrent variceal bleeds, on the other. It is important to recognize, in the first instance, that a patient with known esophageal varices and acute gastrointestinal bleeding has approximately a 50% chance that the bleeding is actually coming from a source other than varices[5]. Lesions such as hemorrhagic gastritis, gastric or duodenal ulcers and Mallory-Weiss tears are other likely etiologies. Diagnostic errors will be quite common unless the most accurate means of assessing the actual site of bleeding are used. This