Improving prognosis following a first variceal haemorrhage over four decades

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Abstract

***Background*—Variceal bleeding is a frequent cause of death in patients with cirrhosis and portal hypertension. Over the past 40 years a number of new techniques have been introduced to control active variceal haemorrhage. Many randomised controlled trials were performed to evaluate these new therapies. While most have demonstrated efficacy in controlling haemorrhage few showed improved survival.**

***Aim*—The aim of this study was to investigate whether the prognosis for cirrhotic patients following a first variceal haemorrhage has improved over the past four decades.**

***Patients and methods*—A total of 1475 patients included in the control or untreated arms of randomised controlled prophylactic trials for the primary prevention of variceal haemorrhage between 1960 and 2000. Twenty eight eligible randomised controlled studies were included. Over the 40 year period of observation there was a reduction in bleeding related mortality over time from approximately 65% to approximately 40% (p=0.024).**

***Conclusion*—This study suggests that there has been a significant reduction in bleeding related mortality in patients with cirrhosis and portal hypertension over the past 40 years.**

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Keywords: portal hypertension; cirrhosis; variceal bleeding; primary prophylaxis; prognosis

Variceal bleeding is one of the most frequent causes of death in patients with cirrhosis and portal hypertension.[1] Approximately 30–50% of cirrhotic patients die within six weeks of a first variceal bleed .[1 2] Over the past 40 years a number of new surgical, pharmacological, endoscopic, and radiological techniques have been introduced to improve the treatment of variceal bleeding. A large number of high quality randomised controlled trials have investigated the efficacy of these new treatment modalities.[3] Many treatments for active variceal haemorrhage have been shown to arrest bleeding or prevent rebleeding, but few claimed to demonstrate improved survival.[3 4] To look at this problem from another viewpoint, we hypothesised that the fate of the control groups in prophylactic trials should reflect the efficacy of contemporaneous treatment for acute variceal bleeding. Prophylactic trials spanning four decades are available and in many cases are of high quality. It is assumed that as participants in controlled trials these patients should have received "state of the art" treatment to arrest haemorrhage. The aim of this study was to determine whether bleeding related mortality changed over the period of observation.

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Methods

Prophylactic trials were identified from literature searches using the Medline database. Studies were also identified from previous reviews, meta-analyses, etc. Studies of the natural history of varices were also reviewed in an attempt to identify well described untreated cohorts of patients. Trials were included if there was a placebo or untreated control group and sufficient information provided in the study to calculate mortality due to bleeding. For each study the number of patients in the control groups was identified. The number of patients in the control group who bled from varices or portal hypertensive causes and the number in whom death was attributed to bleeding were recorded. The severity of the underlying liver disease at the time of randomisation was recorded using Child's or Pugh's grading systems.[5 6]

STATISTICS

Results were analysed using GraphPad Prism (GraphPad software Inc, California, USA). Linear regression with 95% confidence intervals was graphed using GraphPad Prism. Differences in bleeding related mortality were assessed using Fisher's exact test. p values <0.05 were considered significant. Unless otherwise stated, data are expressed as mean (SEM).

Results

Twenty eight studies were identified. A number of studies published in abstract form were excluded because of insufficient data to calculate bleeding related mortality in the control groups.[7–11] Studies of the natural history of oesophageal varices were also reviewed but excluded for similar reasons.[1 12–14] Details of the included studies are shown in table 1. A total of 3105 patients were included, of whom 1475 were in the control groups. The mean number of patients in the control group per study was 52.7 (5). Pugh's or Child's grading was not available in seven studies but was estimated from data supplied in the papers.[15–21] Pugh's grade at entry to the studies was as follows: 502 grade A (34%), 596 grade B (40%) and 377 grade C (26%). Mortality rates ranged from 26% to 83%. The relationship between time and mortality is shown in fig 1. An F test showed that there was a significant fall in

Table 1 Summary of prophylactic trials included in this analysis

Trial	*(n)*	*Pugh's grade A/B/C*	*Mortality*	*Treatment for bleeding*
Jackson 1968*[17]	58	10/23/25	55%	S*
Resnick 1969*[20]	45	19/20/6	42%	SS
Conn1972*[15]	31	10/11/10	50%	Not stated
Conn 1972*[15]	22	0/11/11	83%	SS
Paquet 1982[30]	36	9/11/16	64%	"Active conservative"
Witzel 1985[31]	53	19/25/9	63%	Not stated
Koch 1986[32]	30	16/9/5	70%	Not stated
Wordehoff 1987[33]	24	7/12/5	53%	VP, BT
Pascal 1987*[18]	112	19/41/52	60%	"Standard treatment"
Sauerbruch 1988[34]	65	21/30/14	46%	ES, VP, BT
Piai 1988[35]	69	16/31/22	66%	Som, ES, BT, S
Lebrec 1988[36]	53	29/24/0	50%	ES, VP, BT
Ideo 1988[37]	49	19/19/11	36%	Som, BT
Santangelo 1988*[21]	45	12/17/16	29%	Not stated
Potzi 1989[38]	41	14/14/13	64%	ES
IMPP 1989[39]	89	56/28/5	32%	Drugs, ES, BT
Russo 1989[40]	20	9/8/3	67%	BT, ES
Inokuchi 1990[41]	52	31/21/0	41%	ES, S
Kobe 1990[42]	33	10/17/6	58%	ES
Andreani 1990[43]	41	10/21/10	40%	VP, BT
Triger 1991[44]	35	14/15/6	29%	ES
De Franchis 1991[45]	51	18/22/11	65%	ES
Conn 1991[46]	51	24/24/3	27%	VN, ES
Gregory 1991[47]	138	43/59/36	32%	VP, BT, SS
PROVA 1991*[19]	72	21/22/29	46%	ES
Sarin 1996[48]	33	10/13/10	38%	EVL, ES
Lay 1997[49]	64	16/23/25	26%	Drugs, ES, BT, S
Lo 1999 [50]	63	20/25/18	32%	VP, EVL

*Studies in which Pugh's grading was not given but was estimated from data in original publication.
Emergency treatment for variceal bleeding included: ES, endoscopic sclerotherapy; EVL, endoscopic variceal band ligation; BT, balloon tamponade; SS, shunt surgery; S, surgery; Som, somatostatin; VP, vasopressin; VN, vasopressin+nitroglycerin; S*, transoesophageal ligation of varices in a minority of patients—details of other treatments not given.

bleeding related mortality with an F value of 5.57 and p=0.026. From the regression line it appears that overall mortality fell from approximately 55% to approximately 40% over the 40 year period of observation.

Further analysis by decade was carried out due to concerns about the distribution of the numbers of studies, which ranged from only four in the 1960s and 1970s to 13 in the 1980s and 11 in the 1990s. Mortality in the 1990s was significantly lower than that in the 1980s (p = 0.0055) but not significantly different to the 1960s and 1970s (p=0.12).

Discussion

The results of this analysis suggest that mortality from a first variceal haemorrhage in cirrhotic patients has declined over the past 40 years by approximately a third. Many new treatments and techniques have been introduced over this period, including somatostatin, octreotide, terlipressin, endoscopic sclerotherapy, endoscopic banding, transjugular intrahepatic portosystemic stent shunt, advances in surgical techniques, etc .[3] Advances in intensive care and increasing recognition of the importance of bacterial infections and early appropriate treatment may also help to improve prognosis.[22] There is a long tradition of clinical trials in portal hypertension. With standardisation in terminology and methods of reporting many portal hypertension trials are now recognised to be of particularly high quality.[23] Most clinical trials have shown that these new techniques improve control of active variceal haemorrhage and reduce transfusion requirements. With rare exceptions, significant improvements in survival have not been demonstrated in controlled trials including patients with active variceal haemorrhage.

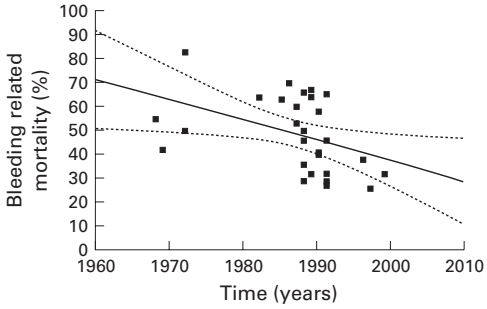

Figure 1 Percentage mortality for patients who bled in the control arms of prophylactic trials over the 40 years, 1960–2000. Bleeding related mortality declined significantly over time, p=0.026. The slope of the regression line is −0.85 ± 0.36 with r=−0.42.

Many of the randomised trials in active variceal haemorrhage were not sufficiently large to demonstrate significant changes in mortality. The largest mortality occurs during the first haemorrhage. Many of the acute trials included patients with recurrent bleeding who tend to have a better prognosis, having already survived an episode of variceal haemorrhage. Patients with massive haemorrhage who die in the prehospital or early hospital phase are also often excluded from these trials.[24] It is interesting that one of the few trials to claim improved survival studied emergency treatment started in the prehospital phase.[4] The relative exclusion of many of these high risk patients may partly explain the difficulty in demonstrating improved survival in active bleeding trials. For this reason we chose to look at the control groups of randomised prophylactic trials. These control groups are as close to an ideal study group as we are likely to get. They received no treatment known to influence variceal haemorrhage and follow up is complete. As participants in clinical trials it is assumed that they received the "state of the art" treatment for variceal haemorrhage once bleeding started (table 1). Because they are first time bleeders they should have a high rate of bleeding related mortality. In addition, deaths from bleeding in the prehospital or early hospital phase are likely to be recorded. However, it is important to realise that these types of data describe overall bleeding related mortality and may reflect a number of factors in addition to treatment received. Other factors such as infection, presence of hepatoma, or portal vein thrombosis may have significant effects on overall mortality.[22 25] These factors are likely to introduce heterogeneity into the results. Nevertheless, the fate of control groups in clinical trials should reflect the effectiveness of the best contemporary treatment available.

Although they are a nearly ideal study group the information available about the control groups is not complete. Standardisation in the reporting of clinical trials is a relatively recent phenomenon and heterogeneity is to be expected in studies reported over four decades.[26] From the original papers it is not always clear whether bleeding related mortality refers to the first bleed or also includes subsequent

recurrent bleeds over a variable period of follow up. Because of the success of prophylactic beta blockers, non-treated control groups in prophylactic trials may become unethical. Meta-analyses have confirmed that prophylactic beta blockers prevent variceal haemorrhage and improve survival.[3 27 28] Beta blockade has become the gold standard against which other prophylactic treatments must be compared. As a consequence it is unlikely that information on further large cohorts of untreated patients with portal hypertension will become available. It may not be possible to extend the current study into coming decades.

A recent study by El-Serag and Everhart lends support to our conclusion that prognosis for variceal haemorrhage has improved.[29] Using the Veterans Affairs patient database they identified two large cohorts of patients treated for an initial variceal haemorrhage between 1981–82 (1339 patients) and 1988–91 (3636 patients). Mortality at 30 days declined from 29.6% to 20.8% (p=0.0001). Interestingly, if the analysis was started 30 days after the initial bleed there was no long term difference in mortality. The authors thus concluded that improved survival was due to improvements in treatment of the initial bleed, most probably the widespread use of injection sclerotherapy. Treatments such as liver transplantation had little impact on outcome as only 12 patients in the latter cohort received this treatment.

In conclusion, study of the control groups of prophylactic trials in portal hypertension suggests that the prognosis for patients with variceal haemorrhage has improved over the past four decades.

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