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Acute variceal haemorrhage in the United Kingdom: Patient characteristics, management and outcomes in a nationwide audit

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ABSTRACT

Background: Despite advances in treatment, acute variceal haemorrhage remains life-threatening.
Aim: To describe contemporary characteristics, management and outcomes of patients with cirrhosis and acute variceal haemorrhage and risk factors for rebleeding and mortality.
Methods: Multi-centre clinical audit conducted in 212 UK hospitals.
Results: In 526 cases of acute variceal haemorrhage, 66% underwent endoscopy within 24 h with 64% ($n = 339$) receiving endoscopic therapy. Prior to endoscopy, 57% ($n = 299$) received proton pump inhibitors, 44% ($n = 232$) vasopressors and 27% ($n = 144$) antibiotics. 73% ($n = 386$) received red cell transfusion, 35% ($n = 184$) fresh frozen plasma and 14% ($n = 76$) platelets, with widely varying transfusion thresholds. 26% ($n = 135$) experienced further bleeding and 15% ($n = 80$) died by day 30. The Model for End Stage Liver Disease score was the best predictor of mortality (area under the receiver operating curve = 0.74, $P < 0.001$). Neither the clinical nor full Rockall scores were useful predictors of outcome. Coagulopathy was strongly associated with rebleeding (odds ratio 2.23, 95% CI 1.22–4.07, $P = 0.01$, up to day 30) and mortality (odds ratio 3.06, 95% CI 1.29–7.26, $P = 0.01$).
Conclusions: Although mortality has improved following acute variceal haemorrhage, rebleeding rates remain appreciably high. There are notable deficiencies in the use of vasopressors and endoscopic therapy. More work is needed to understand the optimum transfusion strategies. Better risk stratification tools are required to identify patients needing more intensive support.

1. Introduction

Cirrhosis of the liver is a major cause of morbidity and mortality globally, accounting for over 800,000 deaths annually worldwide [1] In the United Kingdom (UK) the incidence and prevalence has been rising, with an estimated 8000 new cases per year mainly reflecting increases in alcohol consumption [2]. The formation of gastroesophageal varices is a complication of cirrhosis developing in 50% of cases, the rate dependent upon the severity of underlying disease [3], with subsequent life-threatening acute variceal haemorrhage (AVH) occurring at a rate of 5–15% per year [4].

Three decades ago, the reported short term case fatality following an episode of AVH was in the order of 40–50%, with rebleeding rates of over 30% [5]. The first large scale UK evaluation of outcomes following AVH was conducted twenty years ago. This was a multicentre prospective audit of acute upper gastrointestinal bleeding (AUGIB) reporting data from over 4000 cases of AUGIB from all causes, across 73 hospitals; 4% of presentations were secondary to AVH with an associated in-hospital mortality of 23% [6].

Over the past three decades there have been several developments in the management of portal hypertension and variceal bleeding including early pharmacological therapy with vasopressors [7], use of prophylactic antibiotics [8,9], emergency

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endoscopic therapy [10,11], access to salvage therapy with transjugular intrahepatic portosystemic shunting (TIPS) [12], as well as improvements in general supportive and critical care. Many of these interventions have been incorporated into clinical guidelines. Whilst improved survival following variceal haemorrhage has been reported in several countries over the past two decades [13–16], there is little recent data available to inform practice in the UK in a recent period.

Using data collected as part of a large national audit conducted across the whole of the UK in 2007 [17], we performed this study with the following objectives: (1) to describe the characteristics, processes of care (including the use of pharmacological therapy, endoscopic therapy and use of blood components) and outcomes of patients with cirrhosis and AVH, comparing these where relevant, to recommended best practice as published in clinical guidelines; (2) to make longitudinal comparisons with a previous large UK audit conducted with similar methodology in 1993 [6]; (3) to identify clinical variables associated with rebleeding and mortality; (4) to examine the utility of conventional risk stratification scores in predicting clinically important outcomes following AVH.

2. Methods

2.1. Study methodology and patient population

This is a post hoc analysis of data from the 2007 UK national audit of Acute Upper Gastrointestinal Bleeding (AUGIB) and the Use of Blood [17]. Data were collected prospectively on consecutive, unselected adult admissions with all cause AUGIB over an 8-week period, between May 1 and June 30, 2007. All National Health Service hospitals accepting acute admissions throughout the UK ($n = 257$) were invited to participate in the study of which 212 hospitals (82%) submitted data.

Cases of AUGIB were identified daily from hospital admission units, endoscopy departments, blood transfusion laboratories or adult wards. Detailed information on demography, clinical characteristics, laboratory parameters, resuscitation, use of blood components, endoscopy (timing, diagnosis, stigmata and use of endoscopic therapy), radiological intervention, length of hospital stay and mortality was extracted from hospital records.

The diagnosis of cirrhosis was recorded based upon the clinician's assessment using standard criteria including, clinical evaluation, laboratory results, radiological data or histological findings. Data were also recorded on the presence of ascites and encephalopathy, although grading of severity was not sought as part of the minimum required data-set due to the inherent subjectivity in these assessments; as a result the Child-Pugh score could not be derived. Laboratory parameters to permit derivation of the Model for End Stage Liver Disease (MELD) score were also recorded [18]. High risk stigmata at endoscopy were defined as the presence active bleeding, an adherent clot, nipple sign, or fresh blood in the upper GI tract in the presence of varices. Patients were followed up to 30 days, discharge from hospital or death (whichever came first).

For this analysis we decided a priori to only include those patients with an endoscopically confirmed variceal source of bleeding. A pragmatic definition used in routine clinical practice was utilised for the endpoint of rebleeding, rather than formal consensus criteria for AVH [19,20]. The definition of rebleeding in this study included any component of further haematemesis, passage of fresh melaena, continuing or recurrent hypotension and tachycardia with or without a fall in haemoglobin after the first endoscopy. In addition to being a pragmatic definition, this was an almost identical definition to that used in the previous 1993 UK audit [6]. In hospital rebleeding and mortality, censored at day 30 was also recorded. Definitions are listed in Supplementary Appendix A.

2.2. Statistical methods

Logistic regression models were used to identify clinical variables associated with rebleeding and mortality. Correlation between patients presenting to the same hospital was accounted for using generalized estimating equations. Statistical models were adjusted for a set of potentially confounding variables and potential predictors of rebleeding and mortality, selected from the literature, based upon clinical relevance amongst baseline clinical characteristics, endoscopic findings, pharmacological therapies and admission status, which were all defined a priori [20–25]. These variables were the presence of coagulopathy at admission (defined as an INR > 1.5 and/or PT > 3 s prolonged), platelet count, haemoglobin concentration, urea concentration, age, MELD score, haemodynamic shock, use of an anti-platelet agent (either NSAIDS, clopidogrel, aspirin, dipyridamole or SSRIs), presentation with ascites/encephalopathy, presentation out of normal working hours, in-patient status at the time of bleeding, high risk endoscopic stigmata of haemorrhage (spurting vessel, nipple on varix, adherent clot on varix, fresh blood in the upper gastrointestinal tract).

Two sensitivity analyses were performed; the first investigated the effect of receiving vasopressors on rebleeding and mortality and the second investigated the effect of receiving optimal care (defined as the combination of vasopressors + antibiotics+ endoscopy within 12 h of admission) versus suboptimal care (defined as any combination which did not meet all three aspects of optimum care) upon rebleeding and mortality. In order to investigate the variability across hospitals in the use of vasopressors, the intra-class correlation co-efficient (ICC) was estimated using a mixed-effects logistic regression model, with a random effect for hospital. All sensitivity analyses were adjusted for the same variables as above. The ICC estimates the correlation between hospitals; a larger ICC indicates the use of vasopressors varies between hospitals, while a small ICC indicates there is little variation between hospitals.

Multiple imputation was used to account for missing baseline variables [26]. 20 imputations were performed using the multivariate normal distribution. All baseline variables as well as rebleeding and mortality were included in the imputation model. Continuous variables were analysed using fractional polynomials [27]. All analyses were conducted in Stata version 12.1 (Statacorp, 4905 Lakeway Drive, College Station, TX 77845, USA).

Receiver operating characteristic (ROC) curves were used to evaluate the predictive ability of the MELD score as well as the Clinical and Full Rockall scores for rebleeding, mortality, need for therapeutic intervention and need for early RBC transfusion using SPSS version 20. For the MELD score, ROC curves were constructed only for those patients with all variables to permit calculation of the score.

3. Results

In total, 212 hospitals submitted data relating to 8939 presentations with AUGIB. Of these 1099 did not meet entry criteria and were excluded by the local hospital clinical leads and in a further 1090 cases only minimal data were submitted, due to local reasons, leaving insufficient data for analysis and were therefore excluded by the project group leaving 6750 cases for analysis. Of the 6750 patients, 5004 underwent an in-patient endoscopy, of whom 526 patients with cirrhosis were found to be bleeding from an endosopically proven source of variceal haemorrhage.

3.1. Patient characteristics

Baseline characteristics of the patient population at presentation are summarised in Table 1. The mean age of the cohort was 54.5