HEMODYNAMIC INSTABILITY AND REFEEDING IN PATIENTS WITH GASTROINTESTINAL BLEEDING

Ph.D. Thesis Booklet

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1. INTRODUCTION

1.1. What is the topic?

The topic of my research is gastrointestinal bleeding (GIB), with a particular focus on hemodynamic instability (HI), timing of endoscopy, and early nutritional support. My publications addressed three key aspects: first, a systematic review and meta-analysis quantifying the global burden of shock and HI in GIB; second, an international survey of 533 clinicians to explore how hemodynamic status influences decisions about the timing of endoscopy; and third, a systematic review of randomized controlled trials (RCTs) evaluating the safety of early versus delayed nutrition after upper GIB. Together, these studies provide complementary evidence on how initial patient status and early interventions shape outcomes in GIB.

1.2. What is the problem to solve?

Despite advances in diagnostic and therapeutic endoscopy, GIB continues to carry significant morbidity and mortality. Clinical guidelines provide limited, and

sometimes conflicting, recommendations regarding the management of patients who present with HI, the optimal time for performing endoscopy, and when to safely reintroduce nutrition. These uncertainties result in heterogeneous clinical practices worldwide.

1.3. What is the importance of the topic?

GIB is one of the most common gastroenterological emergencies, with an estimated incidence of 100 per 100,000 population and mortality ranging from 2% to 10%. HI at presentation strongly predicts poor outcomes, including higher mortality, rebleeding, and complications of resuscitation. Furthermore, the management decisions made in the first hours of hospitalization, such as the timing of endoscopy and refeeding, have a major impact on prognosis, length of stay, and healthcare costs. Clarifying these aspects is therefore of high clinical importance, as it directly influences survival and recovery in thousands of patients worldwide each year.

1.4. What would be the impact of our research results?

The implications of our research lie in providing new insights that could shape the future management of GIB. By clarifying the proportion of patients who develop HI and shock, we can better appreciate the burden of this critical condition and emphasize the need for standardized assessment. Investigating the effect of early versus delayed refeeding has the potential to guide safe and efficient nutritional strategies, while exploring the optimal timing of endoscopy according to hemodynamic status can help clinicians tailor interventions to patient stability. Together, these contributions aim to reduce uncertainty in clinical practice, support evidence-based guidelines, and ultimately improve outcomes for patients with GIB.

2. OBJECTIVES

2.1. Study I.

This study aimed to determine the pooled proportion of patients with GIB who develop HI or shock. We further stratified the results by bleeding source and by the timing

of assessment (on admission or during hospitalization). In addition, we collected and summarized all available definitions of HI in the literature.

2.2. Study II.

This international survey sought to investigate how physician characteristics, such as years of clinical practice, hospital type, and annual upper GIB patient volume, influence decisions on endoscopy timing for upper GIB patients. We examined preferences across different hemodynamic conditions, stable, unstable but responding, and unstable non-responding to hemodynamic resuscitation, to better understand variability in clinical practice worldwide.

2.3. Study III.

This meta-analysis of RCTs evaluated the safety and efficacy of early nutrition (EN) versus delayed nutrition (DN) in patients with upper GIB. We analyzed both early and late outcomes, including rebleeding, mortality, and length of hospital stay, and compared results across different bleeding sources. This study aimed to provide

evidence to guide nutritional management after upper GIB.

3. METHODS

3.1. Study I.

This study was conducted according to the Cochrane Handbook and PRISMA 2020 guidelines, with a protocol registered on PROSPERO (CRD42021283258). Eligible studies included RCTs, cohort, and case-control designs reporting HI or shock in adult patients admitted with GIB. A comprehensive search of MEDLINE, Embase, and CENTRAL (to October 14, 2021) was performed without restrictions, using terms covering bleeding sources and hemodynamic instability. Two reviewers independently screened records, extracted data, and assessed inter-reviewer agreement, with disagreements resolved by consensus. Extracted variables included study characteristics, patient demographics, bleeding source, definitions of outcomes, and timing of assessment. Risk of bias was evaluated using the Joanna Briggs Institute Prevalence Critical Appraisal Tool, and the certainty of

evidence was graded with the GRADE approach. Statistical analyses were performed in R (v4.1.2) using the *meta* package. Pooled event rates with 95% confidence intervals (CI) were calculated with a random-effects model, heterogeneity was assessed using I^2.

3.2. Study II.

We conducted a cross-sectional international online survey between April and November 2023 among physicians managing acute upper GIB, including gastroenterologists, surgeons, anesthesiologists, emergency physicians, and intensivists. The survey was developed following a literature review, expert review by 12 international specialists, and pilot testing with 20 physicians. It consisted of four domains with 33 questions, focusing on physician demographics, definitions of HI, and timing of endoscopy under different hemodynamic conditions (stable, unstable responding to resuscitation, and unstable not responding to resuscitation). Data were collected using REDCap at Semmelweis University, and only complete responses were analyzed. The survey was distributed at ESGE Days (Dublin), UEG Week

(Copenhagen), through national and international gastroenterology societies, Endoaula, and professional networks, and was endorsed by multiple European and Latin American societies. Descriptive statistics summarized responses, and group differences were assessed using Chi-square tests. Multinomial logistic regression, performed in R (v4.3.1, *nnet* package), evaluated the effect of physician experience, hospital type, and annual upper GIB volume on endoscopy timing preferences, with statistical significance set at $p<0.05$.

3.3. Study III.

This study followed PRISMA 2020 and Cochrane Handbook recommendations, with the protocol registered on PROSPERO (CRD42022372306). Only RCTs comparing EN versus DN in upper GIB were included. Eligible patients were those with variceal (VUGIB) or non-variceal upper GIB (NVUGIB), and outcomes of interest were early and late rebleeding and mortality, with length of hospital stay and other complications as secondary endpoints. A systematic search of Embase, PubMed, Cochrane Library, Scopus, and Web of Science

(to 27th of August 2023) was conducted without restrictions. Screening, selection, and data extraction were performed independently by two reviewers, with disagreements resolved by consensus. Risk of bias was assessed using the Cochrane ROB 2 tool, and certainty of evidence graded with GRADE. Statistical analyses were performed in R (v4.1.2) using the *meta* and *dmetar* packages. Random-effects models were applied to pool risk ratios (RR) and mean differences (MD) with 95% CIs, heterogeneity was assessed with I^2, and Hartung-Knapp adjustment was applied. Subgroup analyses by bleeding source were planned, with publication bias evaluated by funnel plots and small-study effect tests.

4. RESULTS

4.1. Study I.

In this study, including over six million patients with GIB, approximately one in four developed HI or shock overall, with a pooled event rate of 0.25 (CI: 0.17–0.36). In NVUGIB, the overall proportion was 0.22 (CI: 0.14–0.31), with HI on admission 0.21 (CI: 0.12–0.36) and during hospitalization ranging between 0.10 (CI: 0.08–

0.11) and 0.57 (CI: 0.42–0.70). Shock was 0.36 (CI: 0.21–0.53) on admission and 0.07 (CI: 0.02–0.18) during hospitalization. For VUGIB, the overall rate was 0.25 (CI: 0.19–0.32), with HI on admission 0.38 (CI: 0.12–0.73) and during hospitalization 0.21 (CI: 0.14–0.29) to 0.52 (CI: 0.40–0.63). Shock was 0.26 (CI: 0.18–0.36) on admission and 0.18 (CI: 0.10–0.30) during hospitalization. In lower GIB, the pooled proportion of HI or shock was 0.27 (CI: 0.13–0.49), with HI on admission 0.14 (CI: 0.01–0.81) and during hospitalization 0.49 (CI: 0.27–0.71). Shock ranged from 0.02 (CI: 0.02–0.03) on admission to 0.68 (CI: 0.50–0.82) during hospitalization in severe cases. For peptic ulcer bleeding, the overall event rate was 0.25 (CI: 0.21–0.30), with HI on admission 0.22 (CI: 0.09–0.44) and during hospitalization 0.41 (CI: 0.12–0.78). Shock was 0.25 (CI: 0.19–0.32) on admission and 0.24 (CI: 0.17–0.33) during hospitalization. Finally, colonic diverticular bleeding had the lowest pooled estimate, with an overall rate of 0.12 (CI: 0.06–0.22), HI ranging from 0.05 (CI: 0.02–0.11) to 0.21 (CI: 0.17–0.26), and shock at 0.12 (CI: 0.05–0.26) on admission.

4.2. Study II.

A total of 533 physicians from 50 countries completed the survey, most of whom were gastroenterologists (83.7%), working in Europe (66.6%) and university-based hospitals (54.6%). Two-thirds managed over 100 upper GIB cases annually, and just over half had less than 10 years of clinical experience. While most respondents had access to 24-hour emergency endoscopy (83.1%), only 60.4% routinely used risk scores, and definitions of HI varied, with the majority (64.7%) applying was systolic blood pressure <100 mmHg and heart rate >100 bpm or syncope, or orthostatic hypotension, or signs of organ hypoperfusion. Regarding endoscopy timing, for hemodynamically stable NVUGIB, most physicians (43%) preferred within 24 hours, influenced mainly by hospital case volume. In unstable NVUGIB responding to resuscitation, preferences were more evenly split, though experienced physicians favored earlier intervention. For unstable NVUGIB not responding, nearly half (47.8%) recommended endoscopy within 2 hours, a choice

strongly associated with high-volume centers and senior clinicians.

In stable VUGIB, the majority (29.1%) preferred 12 hours, whereas in unstable VUGIB responding to resuscitation, 37.7% chose 6 hours. For unstable VUGIB not responding, most (60.0%) selected 2 hours, regardless of practice setting, with earlier intervention favored in experienced and high-volume groups. Across all hemodynamic scenarios, significant variability in timing was observed, particularly influenced by clinical experience, hospital type, and patient volume.

4.3. Study III.

This meta-analysis of 10 RCTs with 1,051 patients compared EN and DN after upper GIB. For early rebleeding (within 7 days), EN did not significantly increase risk compared to DN (RR: 1.04, CI: 0.66–1.63), and for late rebleeding (within 30–42 days), there was likewise no significant difference (RR: 1.16, CI: 0.63–2.13). Regarding mortality, early mortality (within 7 days) showed no difference (RR: 1.20, CI: 0.85–1.71), while late mortality (within 30–42 days) tended toward fewer

deaths in the EN group but did not reach statistical significance (RR: 0.61, CI: 0.35–1.06). In terms of secondary outcomes, EN was associated with a shorter length of hospital stay (MD: –1.22 days, CI: –2.43 to –0.01). For other endpoints, including transfusion requirement, bacterial infection, new-onset ascites, and hepatic encephalopathy, there were no significant differences between the groups. Overall, EN appeared safe, did not increase rebleeding or mortality in either the early or late period, and may contribute to reducing hospitalization time.

5. CONCLUSIONS

5.1. Study I.

Our study demonstrates that HI and shock are frequent and clinically significant in patients with GIB. Based on pooled evidence, approximately one in five patients with NVUGIB, one in four with VUGIB, and one in eight with colonic diverticular bleeding develop shock or HI either on admission or during hospitalization. These findings highlight the need for proactive treatment strategies,

standardized assessment, and continuous monitoring to minimize adverse outcomes in this high-risk population.

5.2. Study II.

Our findings reveal a consistent trend: the more hemodynamically unstable the patient, the earlier physicians prefer to perform endoscopy for acute upper GIB. Earlier intervention was particularly favored by more experienced clinicians, those working in university-based hospitals, and physicians managing higher patient volumes. Notably, adherence to international guideline recommendations was suboptimal, especially among clinicians with more than 15–20 years of practice. These results underscore the need to improve consistency in clinical practice and highlight key areas for future guideline development and targeted education.

5.3. Study III.

Compared to DN, EN (within 24 hours) is a safe intervention that reduces the length of hospital stay without increasing the risk of complications such as rebleeding, mortality, newly onset ascites, newly onset

bacterial infections, or blood transfusion requirements following hemostasis of upper GIB.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

One in four patients with gastrointestinal bleeding develops shock or hemodynamic instability: A systematic review and meta-analysis

Obeidat; Mahmoud, Teutsch; Brigitta, Rancz; Anett, Tari; Edina, Márta; Katalin, Veres; Dániel Sándor, Hosszúfalusi; Nóra, Mihály; Emese, Hegyi; Péter, Erőss; Bálint

World Journal of Gastroenterology, 2023 Jul 28;29(28):4466-4480.

DOI: 10.3748/wjg.v29.i28.4466.

IF: 4.3 (2023)

Hemodynamic Status as a Determinant Factor of Optimal Endoscopy Timing in Upper Gastrointestinal Bleeding: Results from an International Survey of 533 Clinicians

Obeidat; Mahmoud, Floria; Diana-Elena, Teutsch; Brigitta, Abonyi-Tóth; Zsolt, Hegyi; Péter, Erőss; Bálint, International Advisory Group of The Survey: Laursen; Stig B., Camus; Marine, Verdonk; Franck, Vincze; Áron, Bognár; Zsolt, Drug; Vasile, Siau; Keith, Gralnek; Ian M.

Gastroenterology, 2025

IF: 25.1

Early nutrition is safe and does not increase complications after upper gastrointestinal bleeding: a systematic review and meta-analysis of randomized controlled trials

Obeidat; Mahmoud, Teutsch; Brigitta, Floria; Diana-Elena, Veres; Dániel Sándor, Hegyi; Péter, Erőss; Bálint

Scientific Reports, 2024 May 10;14(1):10725.

DOI: 10.1038/s41598-024-61543-z.

IF: 3.9 (2024)